

**THE DEVELOPMENT OF A CARE BUNDLE TO IMPROVE THE INITIAL  
MANAGEMENT OF MATERNAL SEPSIS FOR USE IN LOW AND  
LOWER-MIDDLE INCOME COUNTRIES**

by:

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## **ABSTRACT**

### **Aims**

The main objectives for this thesis were:

- To undertake a systematic review to assess the effectiveness of using care bundles in low and lower-middle income countries (LMIC)
- To complete a modified Delphi study to gain consensus on the most important and feasible items to be included in a low-income maternal sepsis bundle
- To develop an exploratory theory of change (TOC) model to assist in planning the implementation of the bundle.

### **Methods**

To achieve the above aims, a number of research methodologies were used including: systematic review & meta-analysis, modified Delphi and undertaking in-country workshops to develop a TOC.

### **Results**

A comprehensive literature search identified 2770 citations, 10 of which were included in the systematic review. Meta-analysis showed the use of bundles significantly reduces the incidence of infection. Consensus was achieved after three iterations of the modified Delphi, with the following final bundle item: Fluids, Antibiotics, Source Control, Transport and Monitoring (FAST-M). Multiple workshops were used to build a TOC diagram.

## **Conclusion**

A low-income maternal sepsis bundle has been produced through international consensus. Framework for an exploratory TOC model has been developed to assist in planning the bundle's implementation. These findings can be used to design an appropriate feasibility study to pilot the bundle.

## **DEDICATION**

*First and foremost, I would like to thank my parents for their continued love and support. Thank you for encouraging me to take this chance and for supporting me during this entire degree. I would not be in the position I am today without you and for that, I am eternally grateful. I dedicate this thesis to you both.*

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## **LIST OF ABBREVIATIONS**

<b>LMIC</b>	Low and lower-middle income countries
<b>IHI</b>	Institute for Healthcare Improvement
<b>SSC</b>	Surviving Sepsis Campaign
<b>CONSORT</b>	Consolidated Standards Of Reporting Trials
<b>TREND</b>	Transparent Reporting of Evaluations with Non-randomized Design
<b>ROBINS-I</b>	Risk Of Bias In Non-randomized Studies - of Interventions
<b>VAP</b>	Ventilator-associated pneumonia
<b>CAUTI</b>	Catheter-associated urinary tract infection
<b>CLABSI</b>	Central line associated bloodstream infection
<b>INICC</b>	International Nosocomial Infection Control Consortium
<b>ITU/ICU</b>	Intensive Therapy Unit/Intensive Care Unit
<b>WHO</b>	World Health Organization
<b>JHPIEGO</b>	Johns Hopkins Program for International Education in Gynecology & Obstetrics
<b>NGO</b>	Non-Governmental Organisation
<b>BEmOC</b>	Basic Emergency Obstetric Care
<b>TOC</b>	Theory of Change

## **CHAPTER 1: THESIS INTRODUCTION AND OBJECTIVES**

## INTRODUCTION

### Background

Maternal sepsis has recently been defined by The World Health Organization (WHO) as, *“a life-threatening condition - defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period”*<sup>1</sup>. It is a recognised major cause of maternal mortality, accounting for over 10% of maternal deaths worldwide<sup>2</sup>. Although this is a complication seen regularly in high-income countries, there are significantly more cases of maternal sepsis identified in low and lower-middle income countries<sup>3</sup>. A recent review in 2014 by the WHO identified that the majority of these deaths occur in Sub-Saharan Africa, accounting for at least 50% of the total deaths from maternal sepsis globally<sup>2</sup>.

Other leading causes of maternal mortality globally include postpartum haemorrhage and hypertensive disorders<sup>2</sup>. As part of the United Nation’s Sustainable Development Goals, the priority has been to work on reducing maternal deaths<sup>4</sup>, and research has primarily been focussed on the above two conditions. However, sepsis is being recognised as a serious and important cause of maternal mortality that requires more attention. It is for this reason that, in 2016, the WHO and Jhpiego developed a taskforce called the *“Global Maternal and Neonatal Sepsis Initiative”*<sup>1</sup>. This collective group of experts’ objective is to promote research and development in the field of maternal and neonatal sepsis, aiming to reduce maternal mortality from sepsis world wide<sup>1</sup>. Their work includes the development of the robust, evidence-based definition for maternal sepsis, which will help healthcare workers in identifying and therefore treating sepsis earlier.

The definition of sepsis in general has also been changed recently, following an international consensus by leading world experts in sepsis in 2016. The aim was to identify an up-to-date definition for sepsis and its classification<sup>5</sup>. Twenty five years earlier, the first definitions of sepsis were developed by an international group of experts, in 1991. At this time, sepsis was identified as the *“host’s systemic response to infection, in the presence of systemic inflammatory response syndrome (SIRS) criteria”*<sup>6</sup>. SIRS criteria included two or more of the following:

- Heart rate >90/bpm
- Respiratory rate >20/bpm
- Temperature >38 °C or <36 °C
- White blood cell count of >12,000/m<sup>3</sup> or <4,000/m<sup>3</sup> or >10% immature forms<sup>6</sup>

Severe sepsis was classified as the presence of sepsis with signs of tissue hypo-perfusion, and septic shock referred to refractory hypotension in the presence of an infection, despite adequate fluid resuscitation<sup>6</sup>.

A decade later, a new taskforce updated the definition but did not alter it significantly<sup>7</sup>. Twenty-five years after the first definition, experts recognised the changes and advances in sepsis research and the same taskforce came together and published *“The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)”*<sup>5</sup>. The findings from the taskforce advise the new definition of sepsis to be as follows, *“life-threatening organ dysfunction caused by a dysregulated host response to infection”*<sup>5</sup>.



The clinical criteria have also been updated, to replace “SIRS” with the “SOFA” score (sequential [sepsis related] organ failure assessment). This tool works on a points based system includes variables such as consciousness level, urine output and blood test results include platelet count and creatinine level, among others. A higher SOFA score indicates higher mortality with a score of 2 or more indicating an in-hospital mortality chance of more than 10%<sup>5</sup>.

A bedside clinical score called q-SOFA (quick-SOFA) has also been developed using three variables only. Patients are likely to have worse outcomes if they have two of the following: a respiratory rate of >22/min, altered mentation and a systolic blood pressure of <100mmHg<sup>5</sup>.

The signs of maternal sepsis can be different to that of a non-pregnant patient and often patients can deteriorate rapidly<sup>8</sup>, therefore it is important for clinicians to be aware of the signs of sepsis, and to have a robust method of initially managing maternal sepsis to improve treatment and reduce mortality rates. This can be further achieved by the use of a sepsis care bundle. The confidential enquiry into maternal deaths (MBRRACE-UK) report in 2014 centred on maternal sepsis, and advised that a sepsis care bundle should be used immediately in the management of a woman presenting with sepsis in pregnancy or the puerperium<sup>9</sup>.

A bundle can be identified as, *“a collective group of evidence based interventions that, when given together, improve overall patient outcomes”*<sup>10</sup>. There should be an all-or-nothing

approach to using a bundle, such that all eligible patients should be managed in the same way to ensure a standardised approach and to receive the most benefit<sup>11</sup>.

Various bundles have been created specifically for use in the management of sepsis. The UK Sepsis Trust developed the “Sepsis Six” care bundle, which radically changed sepsis management for healthcare professionals in the UK<sup>12</sup>. This easy-to-follow bundle comprised of six elements to be carried out within one hour of the suspicion of sepsis, known as “the Golden Hour”<sup>13</sup>. They include the following interventions:

- Administer Oxygen
- Take blood cultures
- Give IV antibiotics
- Give IV fluids
- Check serial lactates
- Measure urine output<sup>13</sup>

It was found that implementing the elements of this bundle in a timely and efficient manner helped to significantly reduce mortality from sepsis in a prospective observational study conducted in the UK<sup>13</sup>. There are also global guidelines including the “Surviving Sepsis Campaign”, which offer both three and six hour bundles, intended to be used in the initial resuscitation and on-going management of sepsis<sup>14</sup>. These bundles include more complex interventions such as administration of vasopressors (if required) and are generally advised to be used in units where critical care facilities are available. None of the above sepsis care bundles have been developed with a low income setting in mind and contain measures that

are unavailable in a majority of health care settings in low and lower-middle income countries<sup>15</sup>.

In low income countries, clinicians have been unable to implement the elements of these kinds of sepsis bundle in the initial management of their patients presenting with sepsis<sup>16</sup>. Specialists in low income countries see it as unsuitable, given the often limited resources available<sup>17</sup>. It is important to ensure mothers living in low and lower-middle income countries will have access to essential care when presenting with signs of sepsis. This can be achieved by creating a care bundle specific to the needs of low and lower-middle income countries. A specialised care bundle for the management of maternal sepsis will provide an evidence-based framework that can be used to commence treatment promptly and safely. This project will address this important global need and help to combat and reduce maternal mortality and morbidity secondary to sepsis.

## OBJECTIVES

The objective of this thesis is to develop a new care bundle, which can be used in the initial management of maternal sepsis, in low and lower-middle income countries.

There are three main chapters in this thesis, outlining the work undertaken to develop this low-income maternal sepsis bundle. These are summarised below:

- Chapter 2: Systematic review & meta-analysis on the efficacy of the use of general care bundles in low and lower-middle income countries
- Chapter 3: Development of the low-income maternal sepsis bundle using a robust, iterative, international Delphi consensus method
- Chapter 4: Development of an exploratory theory of change framework to implement and operationalise the newly created bundle, produced through in-country meetings, which took place in Malawi in May 2016

The longer-term goal, which is outside the remit of this thesis, would be to initially pilot and then formally evaluate, through a clinical trial, the care bundle in a low-income country such as Malawi.

**CHAPTER 2: THE USE OF A CARE BUNDLE IN LOW AND LOWER-  
MIDDLE INCOME COUNTRIES: A SYSTEMATIC REVIEW AND META  
ANALYSIS**

## **ABSTRACT**

### **Objective:**

To review the effectiveness of care bundles in comparison to usual care, in low and lower-middle income countries (LMIC).

### **Design:**

Systematic Review with Meta-Analysis

### **Data Sources:**

Medline, Embase, British Nursing Index, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, BioMed Central, PsycINFO, African Index Medicus, Web of Science and Science Citation Index (from database inception to December 2015) without language restrictions.

### **Review Methods:**

We performed a systematic review of studies that included adult patients in LMIC and compared the use of bundled care to usual care. We selected randomised and non-randomised studies with a variety of clinically important outcomes. The primary outcome included improved care with the use of a bundle. Additional outcomes included incidence of infection & mortality outcomes. Two independent reviewers undertook data extraction and assessed the quality of the included studies. The Cochrane Risk of Bias tool for randomised

and non-randomised studies was used respectively. Data was presented as forest plots with and without summary measures.

### **Results:**

We identified one randomised controlled trial (n=109) and nine before-and-after studies (n=87, 055). All studies were set in LMIC and investigated the use of a variety of different bundles, including those for sepsis, ventilator-associated pneumonia and catheter-associated urinary tract infections (UTI) compared to usual or standard care. Meta-analysis of five studies showed an overall significant reduction in the incidence of infection with bundled care (rate ratio 0.58, 95% confidence interval 0.48 to 0.70,  $p<0.001$ ). Trends in mortality and severity score were also looked at for 3 studies, however these were not meta-analysed.

### **Conclusions:**

The use of a care bundle in LMIC can significantly reduce the incidence of infections. These results may be used to consider developing care bundles for specific use in low resource settings.

**Keywords:** developing countries, low income countries, resource-limited, bundle, patient care bundle, multi-dimensional approach, early goal directed therapy, care package

## INTRODUCTION

A care bundle is defined as a small, straightforward set of evidence-based practices or interventions that, when performed collectively and reliably, improve patient outcomes<sup>10</sup>. The Institute for Healthcare Improvement (IHI)<sup>10</sup> first developed the concept of using a “bundle” initially in a critical care setting back in 2005<sup>18</sup>. A care bundle can be used in a variety of situations and has been adapted to cater for many different medical conditions in a number of specialties<sup>13,19</sup>.

The idea of a bundle is to ensure well established best practices are completed for every patient, every time<sup>10</sup>. This allows consistently high quality care and improves the reliability of the treatment being offered<sup>18</sup>. There is also an “all-or-nothing” element to using a care bundle, with delivery of the complete bundle and adherence to each component being an important factor to a bundle’s success.

Bundles have been used consistently in high-income countries for the past decade with encouraging results<sup>12,14,20</sup>. An important example is the introduction of bundled care in the management of sepsis, which has reduced mortality from sepsis<sup>21</sup>. The Surviving Sepsis Campaign has produced evidence-based guidelines on the management of sepsis<sup>22</sup>, culminating in the formation of two bundles: the 6 hour “resuscitation bundle” and the 24 hour “management bundle”<sup>22</sup>. Between 2005 and 2008, these bundles were implemented voluntarily in 165 sites worldwide, with results being obtained for over 15, 000 patients across Europe, South America and the United States. Results showed an overall reduction in unadjusted hospital mortality from 37.0% to 30.8% by 2 years with the use of the SSC



bundles ( $p < 0.001$ ) and the adjusted odds ratio for mortality also improved the longer a site used the bundles (0.8% per quarter and 5.4% over 2 years [95% confidence interval, 2.5-8.4])<sup>22</sup>.

The use of care bundles has been shown to be effective in improving clinical outcomes in a variety of settings. For instance, Sacks et al showed that the use of a specialised central line care bundle can reduce the incidence of central-line associated bloodstream infections (CLABSIs) in an adult surgical intensive care unit in the United States. With the use of a central line care bundle, the number of CLABSIs reduced from 5.02 to 1.60 per 1,000 catheter days (rate ratio 0.32,  $P < 0.05$ )<sup>23</sup>. This is just one example of the many successfully implemented care bundles being used currently in high-income countries. Unfortunately, in low and lower-middle income countries (LMIC), the implementation of such bundles can be seen as a challenge.

Moreover, further sepsis bundles have been introduced such as “The Sepsis Six” developed in the United Kingdom. This six piece evidence-based bundle aims to facilitate sepsis care within one hour of patients presenting with sepsis<sup>13</sup>. Daniels et al<sup>13</sup> carried out a prospective observational study to compare the delivery of the SSC “resuscitation bundle” in patients managed using “The Sepsis Six” toolkit to those managed without it. They found that there was a decrease in hospital mortality for patients receiving the sepsis six bundle, with a mortality of 20.0% compared to 44.1% of patients who did not receive it ( $p < 0.001$ )<sup>13</sup>. The authors also stated that patients who received the sepsis six bundle were 14.6 times more likely to receive the full SSC resuscitation bundle, suggesting the use of sepsis six

“operationally facilitated” the delivery of the SSC bundle<sup>13</sup>.

In low and lower-middle income countries, delivering all aspects of a care bundle can be difficult for a number of reasons, including a lack of resource availability and difficulty in accessing diagnostic facilities<sup>24</sup>. Baelani et al undertook a study looking at the self-reported availability of resources necessary to implement the SSC guidelines, in 44 respondents from high income countries (such as the United Kingdom and Australia) and 263 respondents from African countries, split into sub-Saharan Africa (encompassing mostly low-income countries) and Mauritius, North Africa and South Africa (countries rated as middle-income countries according to the World Bank). This study found that most resources, including drugs and equipment, were reported as less frequently available by respondents in African countries, compared to high-income countries, especially those in sub-Saharan Africa. Only 1.4% and 1.5% of respondents from sub-Saharan Africa and other African countries [Mauritius, North Africa and South Africa] respectively, were likely to have the resources to implement the SSC guidelines consistently<sup>25</sup>.

Results such as these suggest that low and lower-middle income countries may have more difficulty in implementing care bundles for a variety of reasons. However, given the improvement in care and survival seen with the use of bundles in high-income countries, it is interesting to see if similar results can be achieved when bundles are used in lower-income countries. The aim of this systematic review and meta-analysis is to investigate the effectiveness of using a bundle in improving overall care, in low and lower-middle income countries.

## **METHODS**

### **Data sources and searches**

Databases were searched for relevant literature on the use of care bundles in low and lower-middle income countries (as defined by the World Bank<sup>26</sup>). The studies selected included adult only patients and the use of a care bundle or package, which was defined as: “a small set of key evidence-based practices, that are designed to be completed together, aiming to improve outcomes more than when the components are implemented individually<sup>10</sup>”. The above definition of a bundle, from the Institute of Healthcare Improvement, was used against all studies from the literature search to ensure standardisation of the studies selected.

Medline, Embase, British Nursing Index, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, BioMed Central, PsycINFO, African Index Medicus, Web of Science and Science Citation Index were searched (from database inception to December 2015). Hand searching and checking of reference lists complemented electronic searches. No language restrictions were applied to the search. Search terms were "developing countries", "low income countries" "middle-income countries", "resource-poor", "resource-limited" along with various MeSH terms for low and lower-middle income countries or regions. This was accompanied by the terms "bundle", "patient care bundles", "multi-dimensional approach", "early goal directed therapy", "quality improvement programme" and "care package". The full search strategy used for the Medline search is available in appendix 1.

### **Study selection and data extraction**

Both randomised controlled trials and non-randomised studies were selected. The electronic searches were firstly scrutinised and the full manuscripts of the selected articles were then acquired. Two reviewers (FT and CB) examined the articles and assessed the eligibility of the studies for inclusion. No studies were excluded on the basis of quality. Both reviewers (FT and CB) extracted information from each article including study characteristics, outcome data and quality independently. The primary outcomes included improvement in care and reduction in incidence of infection. Several clinically important secondary outcomes were also extracted including mortality, bundle compliance and a number of process outcomes pertaining to the type of bundle used.

### **Methodological quality assessment**

Once studies were deemed as suitable for inclusion, the quality was assessed by two reviewers (FT and CB). The studies were assessed with tools suitable for the study design. We assessed the randomised controlled trial for adequacy of reporting using the CONSORT checklist<sup>27</sup>. The Cochrane Tool for risk of bias in randomised controlled trials<sup>28</sup> was then used, assessing for selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias. Each category could be classified as low, high or unclear risk<sup>28</sup> (table 1).

The remaining papers were non-randomised studies consisting mainly of before and after interventional studies. For these papers, we used the TREND statement checklist<sup>29</sup> in addition to the ROBINS-I tool by the Cochrane group for the evaluation for the risk of bias in

non-randomised controlled trials<sup>30</sup>. This tool evaluated for confounding bias, selection bias, intervention bias, missing data, measurement of outcomes and selective reporting bias. For each category, it could be classified as low, moderate, serious or critical risk. In order for a paper to be judged as overall low risk, each sub-category is required to be low risk. If there were any categories characterised as moderate risk, the overall risk would be moderate. If one of the categories was given a serious or critical risk outcome, the overall risk would need to be adjusted to reflect this, even if some of the sub-categories were characterised as low risk. Table 2 shows the results of the quality assessment for the nine included studies.

### **Statistical Analysis**

We used the random effects model to pool effect estimates in order to account for the variability in the setting and type of bundle included within the studies. The other popular model used in meta-analysis is the fixed effects model. This is useful in the absence of heterogeneity between the studies. By using the random effects model, it is possible to account for the likely differences in the variety of studies which share common factors but typically differ in ways that will impact the overall result<sup>31</sup>.

Heterogeneity of treatment effects was evaluated using forest plots and the chi squared test, determining the magnitude by computing the  $I^2$  tests. Meta-analysis and forest plots were created using Review Manager 5.3 and STATA 14th Edition statistical software.

**Table 1:** Quality assessment of Andrews 2014<sup>32</sup> using the Cochrane ROB Tool

Domain	Review Author's Judgment
<b>Selection Bias</b>	
Random sequence generation	LOW RISK
Allocation concealment	LOW RISK
<b>Performance Bias</b>	
Blinding of participants and personnel	UNCLEAR
<b>Detection Bias</b>	
Blinding of outcome assessment	UNCLEAR
<b>Attrition Bias</b>	
Incomplete outcome data	LOW RISK
<b>Reporting Bias</b>	
Selective Reporting	LOW RISK
<b>Other Bias</b>	
Other source of bias	LOW RISK

**Table 2:** Quality assessment of nine non-randomised studies using the Cochrane ROBINS-I tool

Study	Domain							Overall RoB Judgement
	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to departure from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results	
<b>Warren 2010</b> <sup>33</sup>	Moderate	Low	Low	Low	No Information	Moderate	Low	Moderate
<b>Alsadat 2012</b> <sup>34</sup>	Serious	No Information	Moderate	Moderate	No Information	Moderate	No Information	Serious
<b>Jacob 2013</b> <sup>35</sup>	Moderate	Low	Low	Moderate	Low	Moderate	Low	Moderate
<b>Jaggi 2012</b> <sup>36</sup>	Serious	No Information	No Information	No Information	No Information	No Information	Critical	Critical
<b>Jaggi 2013</b> <sup>37</sup>	Moderate	Low	Low	Moderate	Low	Low	Moderate	Moderate
<b>Mehta 2013</b> <sup>38</sup>	Moderate	Low	Low	Moderate	No Information	Moderate	Moderate	Moderate
<b>Navoa-Ng 2013</b> <sup>39</sup>	Moderate	Low	Low	Low	No Information	Moderate	Low	Moderate
<b>Mohamed 2014</b> <sup>40</sup>	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
<b>Mukhtar 2014</b> <sup>41</sup>	Moderate	Low	Low	Low	No Information	Moderate	Low	Moderate

## RESULTS

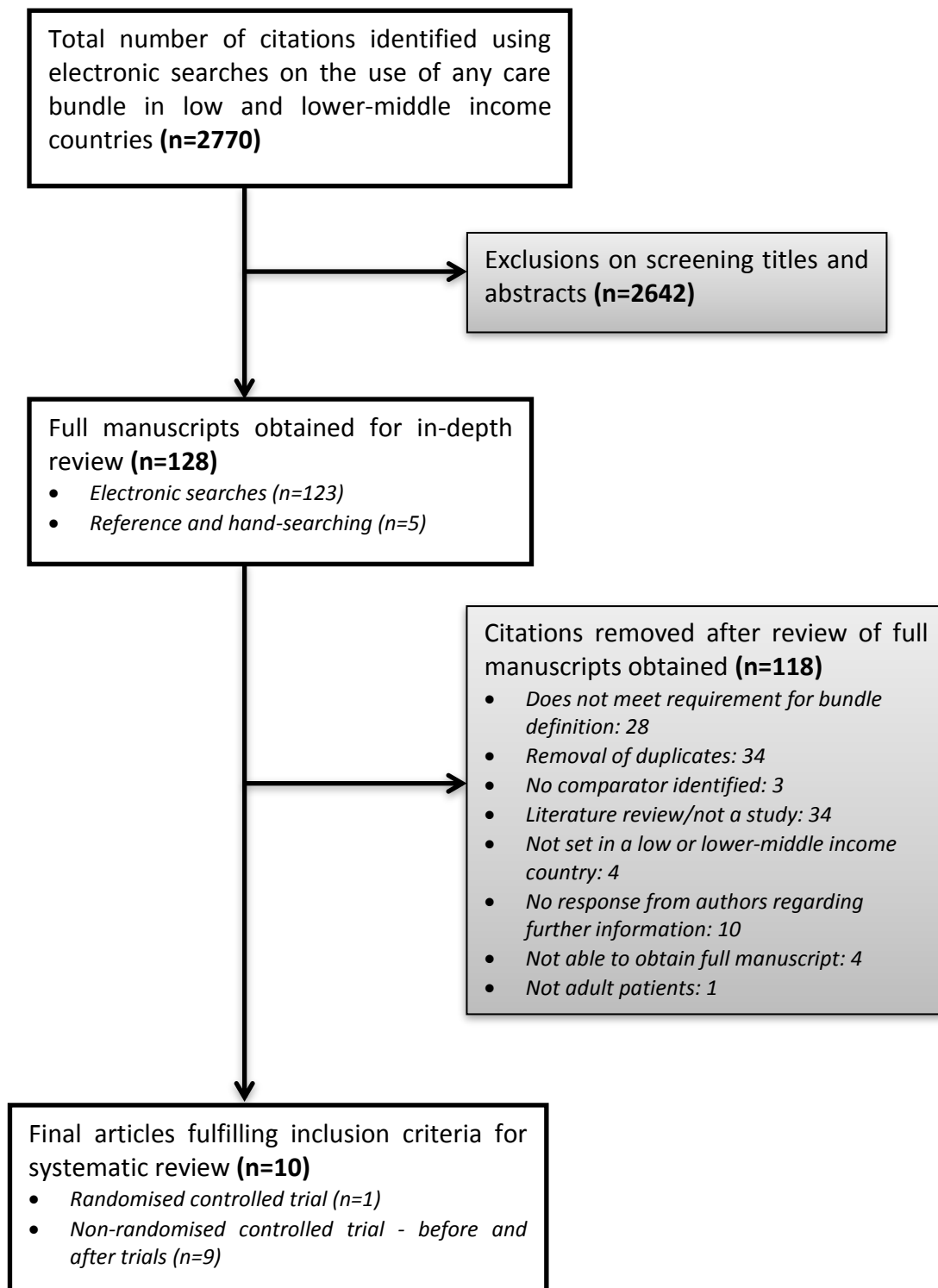
### Results of literature search

Ten studies were included overall, incorporating one randomised controlled trial and nine non-randomised before and after studies, with a total of 87, 164 patients. Figure 1 shows the process of literature search and selection. The characteristics of the ten included studies including study design and setting (country), population, comparators, the types of bundle and inclusion and exclusion criteria are presented in table 3.

All ten studies were set in low and lower-middle income countries; India (3 studies), Egypt (2 studies), The Philippines, Syria, Zambia, Uganda and Kenya. All studies looked at the use of a particular type of bundle compared to usual care in adult patients. Bundles included those for ventilator-associated pneumonia (VAP: 4 studies<sup>34,38,40,41</sup>), sepsis (2 studies<sup>32,35</sup>), catheter-associated urinary tract infection (CAUTI: 2 studies<sup>36,39</sup>), central line-associated bloodstream infections (CLABSI: 1 study) and finally a postnatal care package (1 study).

Table 4 shows the outcomes of the four VAP studies and the outcome findings for the two sepsis studies can be found in table 5. Table 6 shows the important outcomes of the two catheter care bundle studies and finally table 7 outlines the results of the remainder of the studies (postnatal care package and central line bundle).





**Figure 1:** Flowchart of Study Selection

**Table 3:** Characteristics of studies in review

<b>Study, Year (Country)</b>	<b>Study Design</b>	<b>Population</b>	<b>Comparator</b>	<b>Bundle/ Package</b>	<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
<b>Warren, 2010<sup>33</sup>  (Kenya)</b>	Pre-test, post- interventional cross-sectional design	Patients having postnatal consultations from September 2006 to July 2007 (n=163)	Patients seeking postnatal care pre-intervention (n=86)	Kenya post- natal care package	Women seeking post- natal care. No formal criteria documented	No specific exclusion criteria
<b>Alsadat, 2012<sup>34</sup>  (Syria)</b>	Before and after observational design	Patients admitted to ICUs in 4 teaching hospitals (n=unavailable)	Pre-intervention period (no documentation regarding controls therefore n=unavailable)	VAP Bundle	Mechanically ventilated for more than 24h (defined as any 24h period where the patient required any mode of controlled or assisted ventilation) and was > 14 years in age	Patients having intermittent application of continuous positive airway pressure for atelectasis prophylaxis
<b>Jacob, 2013<sup>35</sup>  (Uganda)</b>	Before and after interventional study	Severely septic patients triaged in the Medical Casualty Units in 2 hospitals from May	Observation cohort from separate observational study carried	Early monitored sepsis management bundle	Adults (age ≥ 18 years) with suspected infection; has two of the following: a) axillary temperature	Suspected surgical or obstetric emergency; shock without suspected

		2008 to May 2009 (n=426)	out July to November 2006 (n=245)		>37.5°C or <35.5°C, b) heart rate >90 beats/min, c) respiratory rate >20 breaths/min; systolic blood pressure (SBP) ≤ 100 mmHg; lactate concentration >2.5 mmol/L or Karnofsky Performance Scale (KPS) score ≤40	infection
<b>Jaggi, 2012<sup>36</sup></b> <b>(India)</b>	Before and after study	Adult patients in both ITU and wards with CAUTI from July to December 2009 (n=unavailable)	Pre-intervention patients observed from January to June 2009 (historical controls – n= unavailable)	Catheter Care Bundle	Not formally documented	Not formally documented
<b>Jaggi, 2013<sup>37</sup></b> <b>(India)</b>	Before and after cohort study	All adult patients in ITU from December 2004 to February 2012 (n=31903)	Pre-intervention patients from September 2004 to November 2004 (n=3747)	Central Line Care Bundle	Diagnosis of CLABSI consistent with criteria	No specific exclusion criteria
<b>Mehta, 2013<sup>38</sup></b>	Quasi- experimental	All adult patients in ITU from	Pre-intervention patients from	VAP Bundle and Infection	Diagnosis of VAP consistent with	No specific exclusion criteria

<b>(India)</b>	prospective cohort study	September 2004 to October 2011 (n=42966)	July 2004 to September 2004 (n=3979)	Control Approach	criteria	
<b>Navoa-Ng, 2013<sup>39</sup></b> <b>(The Philippines)</b>	Before and after observational surveillance study	All adult patients in ITU during February 2006 to December 2010 (n=2898)	Pre-intervention patients from December 2005 to February 2006 (n=283)	Catheter Care Bundle and Infection Control Approach	Diagnosis of CAUTI consistent with criteria	No specific exclusion criteria
<b>Andrews, 2014<sup>32</sup></b> <b>(Zambia)</b>	Single-centre non blinded randomised controlled trial (RCT)	All patients presented to the Emergency Department from February to July 2012 (n=49)	Usual care group, randomised (n=54)	Simplified Severe Sepsis Protocol (SSSP)	18 years old or older, met criteria for severe sepsis upon presentation to the emergency department or manifested severe sepsis within 24 hours	Gastro-intestinal bleed, required immediate surgery, suspected congestive heart failure exacerbation end-stage renal disease, raised jugular venous pressure (JVP) more than 3 cm
<b>Mohamed, 2014<sup>40</sup></b> <b>(Egypt)</b>	Before and after interventional study	Adult medical and surgical patients in ICU from September 2012 to August 2013 (n=98)	Pre-intervention patients from September 2011 to August 2012 (n=105)	VAP Bundle	Over 18 years old, mechanically ventilated in ITU for >48 hours	Intermittent application of CPAP for atelectasis prevention,

						patients transferred to another hospital, death within 48 hours of admission, those diagnosed with either PE or GI bleed
<b>Mukhtar, 2014<sup>41</sup></b> <b>(Egypt)</b>	Before and after observational design	Adult medical and surgical patients within the ICU from September 2011 to June 2012 (n=77)	Pre-intervention patients from March 2011 to September 2011 (n=48)	VAP Bundle	Over 18 years old, hospitalised in the ICU due to trauma, mechanically ventilated for at least 48 hours, and met the diagnostic criteria for VAP	No specific exclusion criteria

**Table 4:** Outcomes from VAP bundle studies in review

<b>Study, Year</b>	<b>Incidence of VAP</b> VAP rate = n per 1000 ventilator days	<b>Length of Stay in ITU</b>	<b>Severity Score (APACHE II)</b> Mean Score (+/-SD)	<b>Mortality Rate</b> n/N (%)	<b>Duration of ventilation</b>
<b>Alsadat, 2012<sup>34</sup></b>	Before: 30, 24, 12 After: 6.4, 19, 4.9	-	-	-	-
<b>Mehta, 2013<sup>38</sup></b>	Before: 17.43 After: 10.81 <i>RR 0.62 (95% CI 0.5-.78) p=0.0001</i>	-	-	-	Mean number of days (+/-SD) Before: 1.21 (+/-3.1) After: 1.42 (+/- 5.17) <i>p=0.0001</i>
<b>Mohamed, 2014<sup>40</sup></b>	Before: 26 After: 11	Mean number of days (+/-SD) Before: 15.4 (+/- 5.2) After: 10.8 (+/- 4.9) <i>p=0.036</i>	Before: 21.4 (+/-4.2) After: 20.6 (+/-5.1) <i>p=0.1</i>	Before: 24/105 (22.9) After: 15/98 (15.3) <i>p=0.04</i>	Mean number of days (+/-SD) Before: 12.8 (+/-4.9) After: 8.5 (+/- 4.3) <i>p=0.038</i>
<b>Mukhtar, 2014<sup>41</sup></b>	Before: 42 After: 19 <i>p=0.001</i>	Median number of days (range) Before: 13 (4-78) After: 7 (4-44) <i>p=0.015</i>	Before: 20 (+/- 7) After: 21 (+/-8) <i>p=0.7</i>	Before: 31/48 (64.6) After: 50/77 (64.9) <i>p=0.9</i>	Median number of days (range) Before: 8 (3-49) After: 6 (3-28) <i>p=0.03</i>

**Table 5:** Outcomes from sepsis bundle studies in review

Study, Year	Severity Score (APACHE II)	Mortality Rate	Adverse/morbidity outcomes	Process outcomes
<b>Jacob, 2013</b> <sup>35</sup>	-	Before: 45.7 % After: 33.0% <i>p=0.005</i>	Adverse fluid reactions n/N (%)  Before: Nil After: 56/426 (13.1)	Volume of IV fluids given in first 6 hours - median no. L (range)  Before: 0.5L (0.3-1.0) After: 3.0L (2.5-4.0) <i>p&lt;0.001</i> <hr/> Proportion receiving antibiotics in <1hr - n/N (%)  Before: 73/245 (30) After: 284/426 (67) <i>p&lt;0.001</i>
<b>Andrews, 2014</b> <sup>32</sup>	Mean Score (+/-SD)  Before: 17.9 (+/-0.9) After: 17.8 (+/-0.9) <i>p=0.95</i>	n/N (%)  Before: 34/56 (60.7) After: 34/53 (64.2) <i>RR 1.05 (95% CI 0.79-1.41)</i>	Adverse changes in respiratory status in response to fluids (increase in RR or decrease in SpO <sub>2</sub> ) n/N (%)  Before: 16/56 (28.6) After: 18/53 (34.0) <i>p=0.54</i>	Volume of IV fluids given in first 6 hours - mean no. of L (+/-SD)  Before: 1.6L (+/- 1.1) After: 2.9L (+/-1.0) <i>p&lt;0.001</i> <hr/> Median time to receiving antibiotics from admission – hours (range)  Before: 1.3 (0.4-3.0) After: 1.5 (0.5-3.7) <i>p=0.42</i>

**Table 6:** Outcomes from catheter care bundle studies in review

Study, Year	Incidence of CAUTI CAUTI rate = n per 1000 catheter days	Hand hygiene compliance n/N (%)	Duration of catheterisation Mean no. of days (+/- SD)	Process outcomes
Jaggi, 2012 <sup>36</sup>	Before: 11.4 After: 5.5	Before: 33.0% After: 51.0% <i>p=0.0004</i>	Before: 23 After: 21	-
Navoa-Ng, 2013 <sup>39</sup>	Before: 11.00 After: 2.66 <i>RR 0.24 (95% CI 0.22-0.53)</i> <i>p=0.0001</i>	Before: 297/519 (57.23) After: 2872/3672 (78.21) <i>RR 1.37 (95% CI 1.21-1.54)</i> <i>p=0.0001</i>	Before: 2.9 (+/-4.1) After: 2.73 (+/-4.2) <i>p=0.52</i>	Correct positioning of the catheter (thigh) – n/N (%)  Before: 389/936 (41.56) After: 7485/8425 (88.84) <i>RR 2.14 (95% CI 1.93-2.37) p=0.0001</i>  Urine bag in hanging position – n/N (%)  Before: 389/936 (41.56) After: 7775/8425 (92.28) <i>RR 2.22 (2.01-2.46)</i> <i>p=0.0001</i>



**Table 7:** Outcomes from remainder of studies in review

Study, Year	Incidence of infection CLABSI rate = n per 1000 central line days	Hand hygiene compliance n/N (%)	Duration of central line catheterisation mean no. of days (+/- SD)	Process outcomes
Warren, 2010 <sup>33</sup>	-	-	-	Total quality of care scores for maternal health (0-23) Before: 3.26 After: 8.27 <i>p</i> <0.01 Total quality of care scores for new born health (0-11) Before: 3.37 After: 6.45 <i>p</i> <0.01
Jaggi, 2013 <sup>37</sup>	Before: 6.4 After: 3.9 <i>RR</i> 0.61 (95% <i>CI</i> 0.46-.81) <i>p</i> =0.0007	Before: 1467/ 2013 (73) After: 17914/21327 (84) <i>RR</i> 1.15 (95% <i>CI</i> 1.1-1.22) <i>p</i> =0.0001	Before: 2.53 (+/- 4.4) After: 2.54 (+/-5.8) <i>p</i> =0.9	-

### **Description of studies**

Only one randomised controlled trial met the inclusion criteria. Andrews et al<sup>32</sup> randomised patients admitted to the emergency department, intensive care unit and medical wards of the national referral hospital in Lusaka, Zambia to receive either usual care or their early goal-directed protocol, entitled “Simplified Severe Sepsis Protocol” which included fluids, antibiotics and dopamine +/- blood transfusion as required. The study was terminated early due to problems with respiratory distress secondary to fluids<sup>32</sup>. In the non-randomised sepsis bundle study by Jacobs et al set in Zambia, negative reactions to fluids were also seen as a common adverse effect.

There were nine non-randomised before and after studies included in this review. Three of the nine studies<sup>37,38,39</sup> used a selected “multi-dimensional approach” from the International Nosocomial Infection Control Consortium (INICC),<sup>42</sup> a global scientific network whose work involves assessing the success of a variety of bundles in a mixture of high and low-income settings to reduce the incidence of healthcare associated infections. The INICC supports hospitals in low-income countries, in the implementation of programs to reduce healthcare-associated infection rates. It provides the necessary paperwork and guidance, as well as scientific support to hospitals undertaking studies assessing the use of these bundles. All three INICC studies used the same format in terms of methodology and outcome reported, with patients selected from ICUs in a number of centres. Each paper reported on the use of one bundle including: a VAP bundle in India<sup>38</sup>, a catheter care bundle in The Philippines<sup>39</sup> and a central line bundle in India<sup>37</sup>.

The remaining five studies with an infection bundle intervention were locally designed, with a bundle created specifically for their hospital and setting. Results were reported differently for each study however there was commonality in the outcomes measuring including incidence of infection (VAP, CAUTI or CLABSI). This was measured using a standardised rate formula: *rate = n per 1000 ventilator or catheter or central line days*<sup>34,36–41</sup>

Other common outcomes included the duration of line placement (ventilation/catheterisation/central)<sup>36–41</sup>, in addition to length of stay in the intensive care unit (ICU)<sup>40,41</sup> and severity score measurement<sup>32,40,41</sup>. Four studies looked at mortality rate<sup>21,26,27,32</sup> and three studies identified changes in hand hygiene compliance with the use of a bundle<sup>36,37,39</sup>. Adverse outcomes to the bundle and some process outcomes, such as volume of fluids given and time to antibiotics, were also identified in a number of studies<sup>32,33,35–37,39</sup>.

Of the ten studies included, one study described the use of a postnatal package for client-patient relationships, and compared it's use to the current care that postnatal women receive in rural Kenya<sup>33</sup>.

### **VAP bundle studies**

All four VAP bundles contain similar components. There are seven main components to the VAP bundles used in these studies, including:

1. Positioning (including head of bed elevation)<sup>34,38,40,41</sup>

2. Oral care (e.g. chlorhexidine application)<sup>38,41</sup>
3. Daily assessment for extubation (including spontaneous breathing trial)<sup>34,38,40,41</sup>
4. Gastric care (i.e. peptic ulcer prophylaxis)<sup>34,38,40,41</sup>
5. Deep Vein Thrombosis prophylaxis<sup>34,40,41</sup>
6. Daily sedation break<sup>34,38,40,41</sup>
7. Equipment hygiene (including maintaining endotracheal cuff pressure, removing condensate and using sterile water to rinse respiratory equipment)<sup>38</sup>

None of the four VAP studies included every VAP bundle item. Mukhtar 2014 included all items apart from equipment hygiene<sup>41</sup> and Mehta 2013 omitted DVT prophylaxis and daily sedation break<sup>38</sup>. Both Mohamed 2014 and Alsadat 2012 did not include equipment hygiene and oral care as part of their bundles<sup>34,40</sup>.

The Alsadat paper does not give clear information on the number of patients included and is not clear on the timeline of introduction of the intervention in its numerous sites therefore fewer results were available from this study<sup>34</sup>.

### **Sepsis bundle studies**

The two sepsis care bundle studies took place in Africa, one in Zambia<sup>32</sup> and the other in Uganda<sup>35</sup>. The bundles were slightly different in terms of the elements included; however the patient characteristics for both studies were quite similar. Both studies included adult patients in emergency departments over 18 years old with documented signs of sepsis or severe sepsis<sup>32,35</sup> and identified similar outcomes as shown in table 5.

### **Catheter care bundle studies**

There were two studies identified using a catheter care bundle, Jaggi 2012 set in India<sup>36</sup> and Navoa-Ng 2013 set in The Philippines<sup>39</sup>. Some results from Jaggi 2012 were provided within the paper, however the overall number of patients and statistical analysis was not available, therefore it was difficult to correctly analyse the data further<sup>36</sup>. Outcomes reported were similar for both studies, as seen in table 6 and the incidence of infection was significantly reduced with the use of a catheter care bundle in Navoa-Ng's study<sup>39</sup>.

### **Study Quality**

The randomised controlled trial, Andrews 2014<sup>32</sup> scored highly when assessed using the CONSORT statement extension, showing good reporting quality<sup>32</sup>. Upon quality assessment review using the Cochrane tool for risk of bias assessment for randomised controlled trials<sup>28</sup>, it was found to be overall "low risk" as shown in table 1.

The non-randomised studies were assessed using the TREND statement reporting tool<sup>29</sup> and the Cochrane tool for assessing risk of bias in non-randomised interventional studies<sup>30</sup>. The studies achieved scores of between 19 to 42 out of 57, according to the TREND statement. For several studies, there was lack of detail on eligibility criteria, details of the bundle itself, sample size and clear summarised outcomes.

Quality assessment was assessed using the ROBINS-I tool by the Cochrane group for the evaluation for the risk of bias in non-randomised controlled studies<sup>30</sup>. As seen in table 2, the majority of studies were classed overall as having a "moderate" bias, which is expected of

most non-randomised studies, according to the Cochrane tool<sup>30</sup>. Areas that demonstrated good quality included bias in selection of participants and classification of interventions, which were mostly classed as low and moderate bias. However, one study received an overall classification of “serious” bias and one study was classed as “critical”, the implications of which are explored further in the discussion.

### **Incidence of Infection**

Seven studies reported on the incidence of infection when using a bundle, compared to usual care<sup>34,36–41</sup>. Of these, five studies were included in a meta-analysis<sup>37–41</sup> as two studies did not report adequate data and therefore could not be included<sup>34,36</sup>. The meta-analysis showed a significant reduction in the incidence of infection with the use of a bundle compared to usual care (rate ratio 0.58, 95% confidence interval 0.48 to 0.70,  $p < 0.001$ , figure 2). Evidence of heterogeneity between the papers was low and not significant. ( $I^2 = 9.7\%$ ,  $p = 0.351$ ).

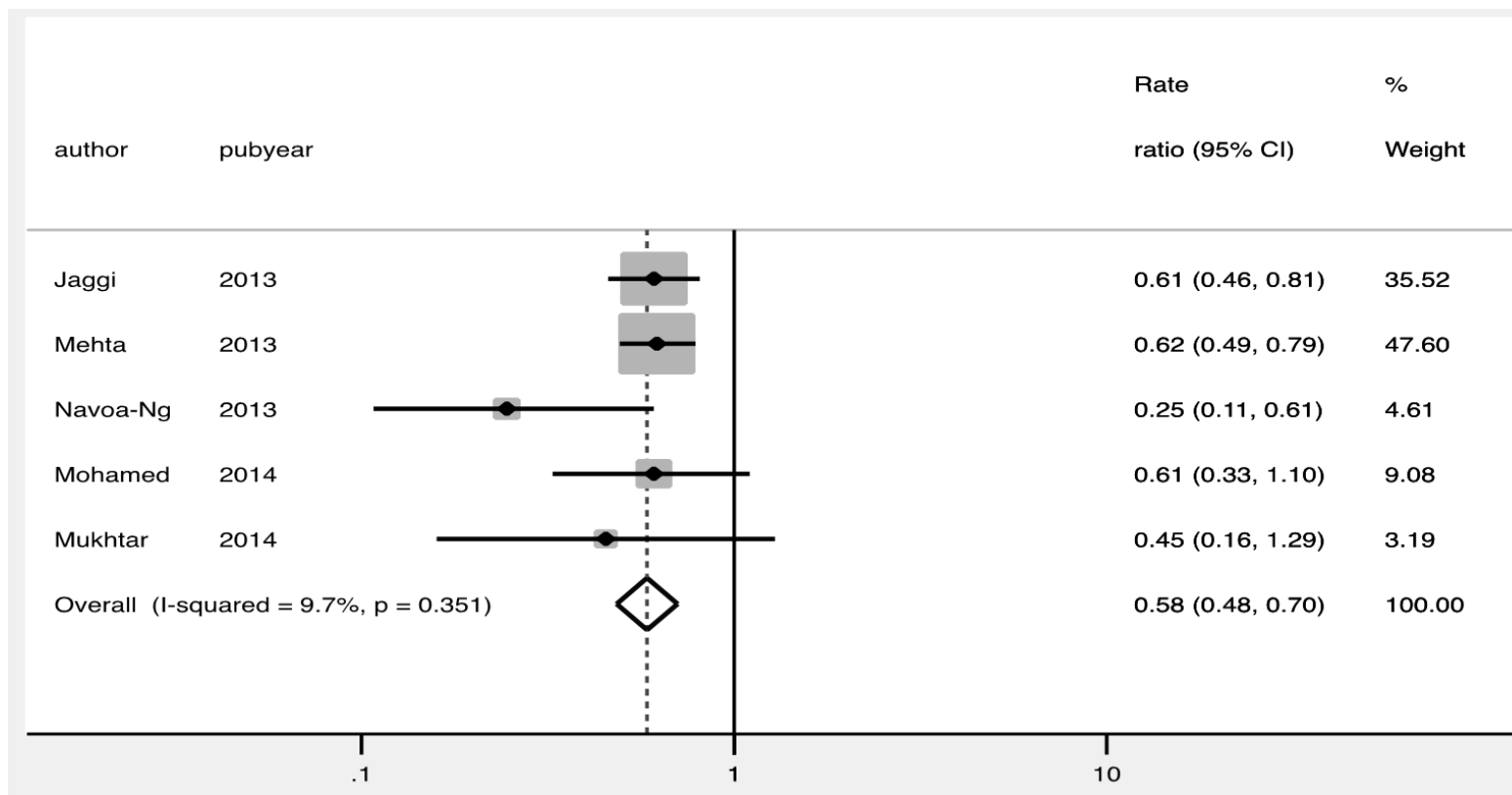
### **Mortality**

Mortality rate was reported in 4 studies<sup>32,35,40,41</sup>. One study was excluded from the meta analysis due to the limitations in the data provided<sup>35</sup>. Of the three studies that were included, two were before and after studies<sup>40,41</sup> and one was a randomised controlled trial<sup>32</sup>. Given the difference in study design, it was decided to display the results in a forest plot without summary measures as opposed to carrying out a meta-analysis (figure 3). This suggests no mortality benefit with the use of the bundle although this has been assessed

further statistically and it is not possible to document whether these results are significant or not. Only one study reported a significant mortality reduction with the use of a bundle<sup>40</sup>, however without meta-analysis of numerous studies we are unable to analyse this further.

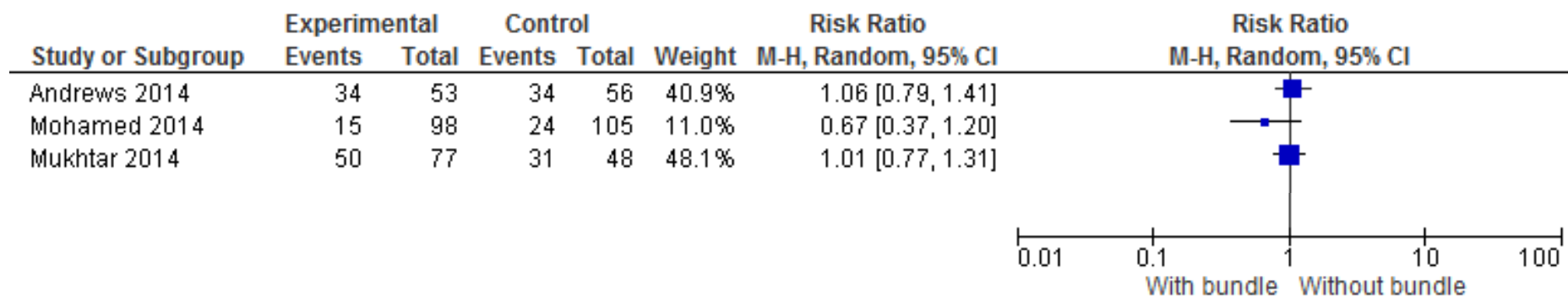
### **Severity Score (APACHE II)**

Three studies reported the illness severity score (APACHE II), given to patients both before and after the use of a bundle<sup>32,40,41</sup>. Similarly, due to study design differences, these were not meta-analysed and the data is presented in the form of a forest plot (figure 4). The figure suggests no reduction in the APACHE II score with the use of a bundle.

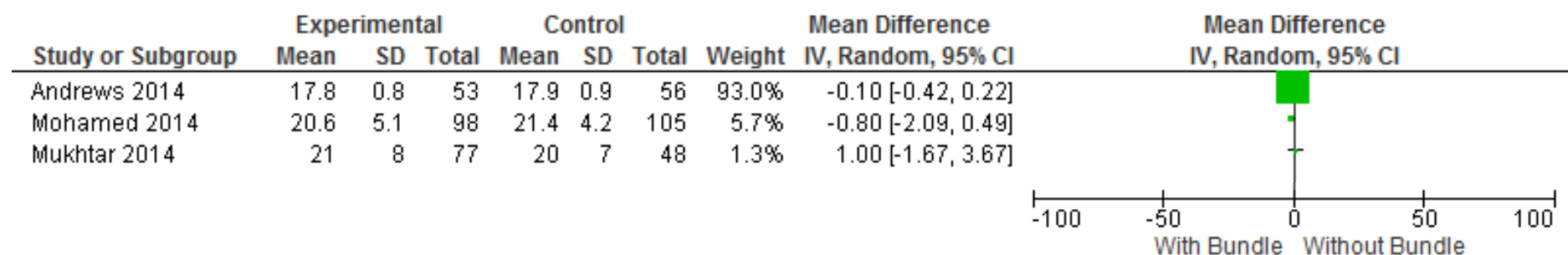


**Figure 2:** Incidence of infection using bundled care compared with usual care





**Figure 3:** Mortality rate using a bundle compared with usual care



**Figure 4:** Severity score with the use of a bundle compared to usual care

## **DISCUSSION**

### **Main findings of the review**

In this systematic review, we looked at the use of different care bundles in low and lower-middle income countries, compared to usual care. In total, ten studies were included from seven low and lower-middle income countries. A number of outcomes were comparable for the variety of interventions included within this review. Meta-analysis showed that there was a statistically significant reduction in the incidence of infection in five of the nine studies that compared the use of a bundle to usual care in the management of various infections (rate ratio 0.58, 95% confidence interval 0.48 to 0.70,  $p < 0.001$ ). There was no evidence of improvement demonstrated in mortality or severity score with the use of a bundle from three studies with different study designs.

### **Strengths and limitations of the review**

Studying the literature, there are no published systematic reviews looking at the use of care bundles, compared to usual care in low and lower-middle income countries. However, over the last ten years, there have been a number of important systematic reviews published looking into the use of care bundles in the management of sepsis, although mainly in a high-income country setting. A systematic review of studies conducted in the USA in 2010 looked at the use of bundled care in septic shock and identified eight studies in total (a mix of RCT and observational studies). Their results were significantly in favour of the use of a sepsis bundle in patients with septic shock with a significant increase in survival noted (odds ratio 1.91, 95% confidence interval, 1.49-2.45,  $p < 0.001$ ). The use of a sepsis bundle was also

associated with a decrease in the time to antibiotics and increase in the appropriateness of prescribing of antibiotics ( $p < 0.0002$ )<sup>43</sup>.

Looking at the prevention of infection using bundles, a recent systematic review published in 2014 looked at 41 before and after studies using a quality improvement initiative such as a care bundle or checklist for the prevention of central line associated bloodstream infections (CLABSIs). The authors found that there was a significant infection rate decrease with the use of a care bundle or checklist (odds ratio 0.39, 95% confidence interval 0.33-0.46,  $p < 0.001$ ). Interestingly, further meta-analysis of results showed an ongoing reduced infection rate up to three months post-intervention (odds ratio 0.30, 95% confidence interval 0.10-0.88,  $p = 0.03$ )<sup>44</sup>.

One of the main strengths of our review is that although the studies included varied in terms of location and intervention used, the majority of papers were comparable and this allowed us to draw important conclusions within the review. A number of studies used similar interventions, allowing us to compare results in different countries and cohorts. Our review is one of the first to explore the relationship between the use of a bundle compared to usual care, in LMIC and we have grouped together all studies using bundles in a number of LMIC including India, Syria, Egypt, The Philippines, Zambia, Uganda and Kenya<sup>32-41</sup>. This allowed us to explore results from these two continents, however these may not be generalisable to all LMIC in other continents. Despite the difference between the countries, most of the studies concluded the use of a bundle was associated with improved care overall, compared to usual care.

Another strength of the review is the overall sample size. Although only 10 studies were incorporated, the meta-analysis included a large enough number of patients (86,224 from the five studies included in the meta-analysis) to show a significant reduction in the incidence of infection. This large number of patients also helps outweigh many of the design issues associated with the studies selected.

The random effects model was also used, to account for the bias which is routinely a problem in observational studies<sup>46</sup>. In terms of bias in our review, the one randomised controlled trial (RCT) that was included in the review was found to be “low” in most bias domains according to the Cochrane Tool (table 1). The remaining nine studies were non-randomised with a before and after design, therefore there is more potential for bias. Many of the before and after studies recognised the limitations attributed to the study design, and one example is the “Hawthorne effect”, cited by Jaggi 2013<sup>37</sup>, Navoa Ng 2013<sup>39</sup> and Jacobs 2013<sup>35</sup>. This refers to the change in behaviour (usually unconsciously) by patients taking part in observational research<sup>46</sup>. The Hawthorne effect is important as it can have a confounding effect on the results and affect the generalisability<sup>46</sup>.

In addition, the use of historical controls (such as those used in Jacobs 2013<sup>35</sup>) has been acknowledged to over-estimate the benefit of a new intervention and may in fact provide misleading results.

On assessing the methodological quality of the non-randomised studies using the Cochrane ROBINS-I tool, there was a moderate to serious risk of bias for confounding for all studies, all of which had a before and after design (table 2).

Two studies showed higher levels of bias overall and this was due to the methodology and reporting of results. Alsadat's study carried out in Syria, looking at the use of a VAP bundle<sup>34</sup>, received an overall bias score of "serious". Reasons for this include minimal information about the study population including the total number of patients recruited and the actual number of patients who developed a ventilator associated pneumonia, both before and after the introduction of the VAP bundle<sup>34</sup>. Percentages were supplied, however without the raw figures, there is clear risk of bias in the selection of the reported results.

Similarly, the study by Jaggi looking at the use of a catheter care bundle in India<sup>36</sup> scored highly, with an overall bias assessment of "critical". Again, there is minimal information provided within this paper and the authors fail to clarify the components of the catheter care bundle, making it difficult to compare with other studies. In addition, due to limitations in the data provided, there is a high risk of bias in both the selection of the reported results and confounding. Numerous attempts were made to contact authors from both papers (Jaggi 2012<sup>36</sup> and Alsadat 2012<sup>34</sup>) to elaborate on the bundles used and numbers of patients, but unfortunately no reply was received. As per the ROBINS-I tool, a "serious" or "critical" result tells the reader that the study at hand has some *"important problems"* or is *"too problematic to provide any useful evidence and should not be included in the synthesis"* respectively<sup>30</sup>. It is therefore more difficult to assess the external validity of these studies

and the use of them in further synthesis should be avoided, as to prevent skewing of the results.

Another limitation of our review is the patient population selected, especially when comparing mortality. From the four studies that compared mortality, two studies included patients only within the ICU<sup>40,41</sup>. The other two studies compared patients presenting to Medical Casualty<sup>35</sup> and Emergency Departments<sup>32</sup>. Patients requiring intensive care treatment tend to be more unwell and therefore these patients may have had a poorer prognosis, which could affect the overall mortality rate and therefore this needs to be considered when taking into account the results<sup>48</sup>.

Moreover, this is an important point when thinking about how these results translate to other settings within a low and lower-middle income country. The majority of the studies included in this review looked at bundles related to nosocomial infections in intensive care settings in a LMIC. Therefore, in more resource limited settings such as a health centre or district hospital in a LMIC, it is difficult to extrapolate the same results. Intensive care units in LMIC are usually found within tertiary hospitals and therefore they may have access to a number of facilities which can improve implementation of such infection bundles. These may include but are not limited to: an increased number of staff, more experienced clinicians e.g. physicians/surgeons and access to more advanced diagnostic tests or interventions that may not be available in a health centre or district hospital.

### **Study implications & conclusions**

Our findings suggest that using a bundle in a low or lower-middle income country significantly reduces the incidence of infection compared to usual care. This review demonstrates care bundles have been used successfully in numerous LMIC and for patients with a variety of conditions. However, our review only includes 10 eligible studies and we were not able to meta-analyse the results for mortality and severity score to show if there was a significant effect with using a bundle due to variations in study design. Further research should be undertaken with a detailed meta-analysis of numerous studies with similar study designs to assess whether the use of a care bundle in an LMIC could help to reduce mortality.

Given the results from our review, there is scope for the development of LMIC-specific bundles for the management of various infections and sepsis. A bundle, which is tailored to meet the needs of low and lower-middle income countries, can help to provide a framework for managing these conditions and improve the care that these patients receive.



**CHAPTER 3: DEVELOPING A BUNDLE TO IMPROVE MATERNAL  
SEPSIS CARE IN LOW RESOURCE SETTINGS: AN INTERNATIONAL  
DELPHI CONSENSUS**

## **ABSTRACT**

### **Objective:**

To develop a consensus based care bundle for use in the initial management of maternal sepsis in low and lower-middle income countries (LMIC).

### **Methods:**

A systematic search of the literature was completed to create a long-list of possible bundle elements. This information was applied to create a comprehensive long-list of contents for inclusion in the bundle. A modified three-iteration Delphi method was used to gain consensus on the final components. Members of an advisory panel offered advice on the contents and questions prior to commencing the Delphi. For round 1, an online questionnaire was sent to a practitioner panel of healthcare professionals working in LMIC. Participants were asked to rank each element on a Likert scale out of 5 on both importance as well as feasibility (in a health centre and hospital setting). In round 2, the same questionnaire was sent to a panel of selected international experts in the field. Further consensus was built with feedback from meetings with the World Health Organization (WHO) maternal sepsis working group. Round 3 of the Delphi involved feeding back the results from the first two rounds to all participants, to identify if consensus had been reached.

**Results:**

In total, 143 LMIC practitioners from a number of different cadres in 34 different LMIC responded to the round 1 survey; in addition to the 11 members of the international expert panel. There was consensus between the views of the practitioners and experts with the same items appearing as the most important. Both groups also deemed these items feasible. The final items selected were: Fluids, Antibiotics, Source Control and Transport (to appropriate higher-level care facility). Monitoring for both mother and baby also scored highly, completing the bundle. These final elements were subsequently summarised with the acronym FAST-M to assist practitioner recall.

**Conclusions:**

A clinically relevant and feasible maternal sepsis care bundle has been developed by international consensus. This can be developed into a package to be implemented and tested in an appropriate setting.

**Keywords:**

low income, lower-middle income, bundle, care bundle, maternal sepsis, sepsis, Delphi, consensus

## INTRODUCTION

Sepsis is the third most common direct cause of maternal mortality, accounting for 10% of maternal mortality worldwide, but is a contributing factor in multiple other causes of maternal death<sup>2</sup>. As mentioned in chapter one, the definitions for sepsis have recently changed to reflect the ongoing developments in sepsis care research over the last ten years. These new definitions and criteria were produced to help improve sepsis recognition and its management world-wide and have shown to be especially useful in treating sepsis.

Maternal sepsis can occur in women during pregnancy or the puerperium and is a challenge due to the differing physiology of women during pregnancy; meaning determining levels of organ dysfunction can be difficult<sup>8</sup>. Therefore having a robust definition, such as the one recently developed by the WHO<sup>1</sup>, can offer clinicians a way of identifying these women and initiating treatment rapidly.

In order to manage sepsis effectively, a number of care bundles have been produced that have been used with success, specifically in high-income countries. Examples include the “Surviving Sepsis” campaign and “Sepsis Six”, which have demonstrated an impressive and consistent ability to nearly double survival through the introduction of care bundles<sup>21,43</sup>. These have not yet been adapted for a maternal population, and the resources do not generally exist to implement the existing bundles in low-income settings. A bundle specifically designed for use in low and lower-middle income countries can standardise and improve the care that pregnant women receive. It may also help decrease mortality from sepsis during pregnancy and the puerperium.

To develop this bundle, we proposed to form consensus and elicit the views of practitioners and experts in the field using a modified Delphi technique. Consensus forming methods aim to bring groups together in order to agree on a certain action or decision<sup>49</sup>. The Delphi method involves members of the groups completing questionnaires or being interviewed in order to narrow down the material offered to agree on a conclusion. Participants then review a report of results and can further amend or justify their responses.

Thangaratnam describes the Delphi method as *“a way of obtaining a collective view from individuals about issues where opinion is important”*<sup>50</sup>. The anonymity of stakeholders is important and the identity of Delphi members should not be revealed to others undertaking the questionnaires, to reduce the risk of bias and the subsequent effects on the answers. The Delphi technique is often composed of a number of iterations (usually between two to three) until a consensus and decision is made. It has been used in a range of situations in clinical practice, for example in creating evidence based guidelines for use in many different medical specialties, including Obstetrics and Gynaecology<sup>50</sup>.

The aim of this study is to use the Delphi method to develop a consensus and evidence-based maternal sepsis bundle, optimised for use in low and lower-middle income countries. We want to ensure the bundle is: suitable to integrate with existing practices; easy to implement; practical enough to initiate in both a health centre and hospital setting and suitable for use in women during pregnancy and the puerperium, presenting with signs of maternal sepsis.

## **METHODS**

We undertook a modified three-iteration Delphi study to gain consensus on the most appropriate items to be included in the low-income country maternal sepsis bundle. The process comprised of three rounds. The first iteration included a consultation with a broad panel of practitioners who care for women with maternal sepsis, in low and lower-middle income countries (LMIC). This was followed by seeking the opinion of a group of selected experts in the field and a final round comprising of further consultation with all participants to ascertain their final opinions on the chosen components of the bundle.

### **Selection of Delphi Items**

In order to determine the various items that may be included for consideration in the Delphi, the steering committee undertook a systematic search of the literature. A comprehensive long-list of possible contents was compiled by reviewing all current literature on sepsis in low and lower-middle income countries, as well as consulting many books, guidelines and protocols from a number of countries including the UK, India, Tanzania and Malawi. Multiple resources were used until saturation had been reached<sup>6–8,16,17,19,20,25,51–135</sup>

The items were grouped into the following categories: Fluids, Monitoring, Breathing, Positioning, Source Control, Prophylaxis, Recovery, Resources, Drugs, Communication and Diagnosis. The initial list was analysed by the steering committee, which removed duplicates and grouped similar items.

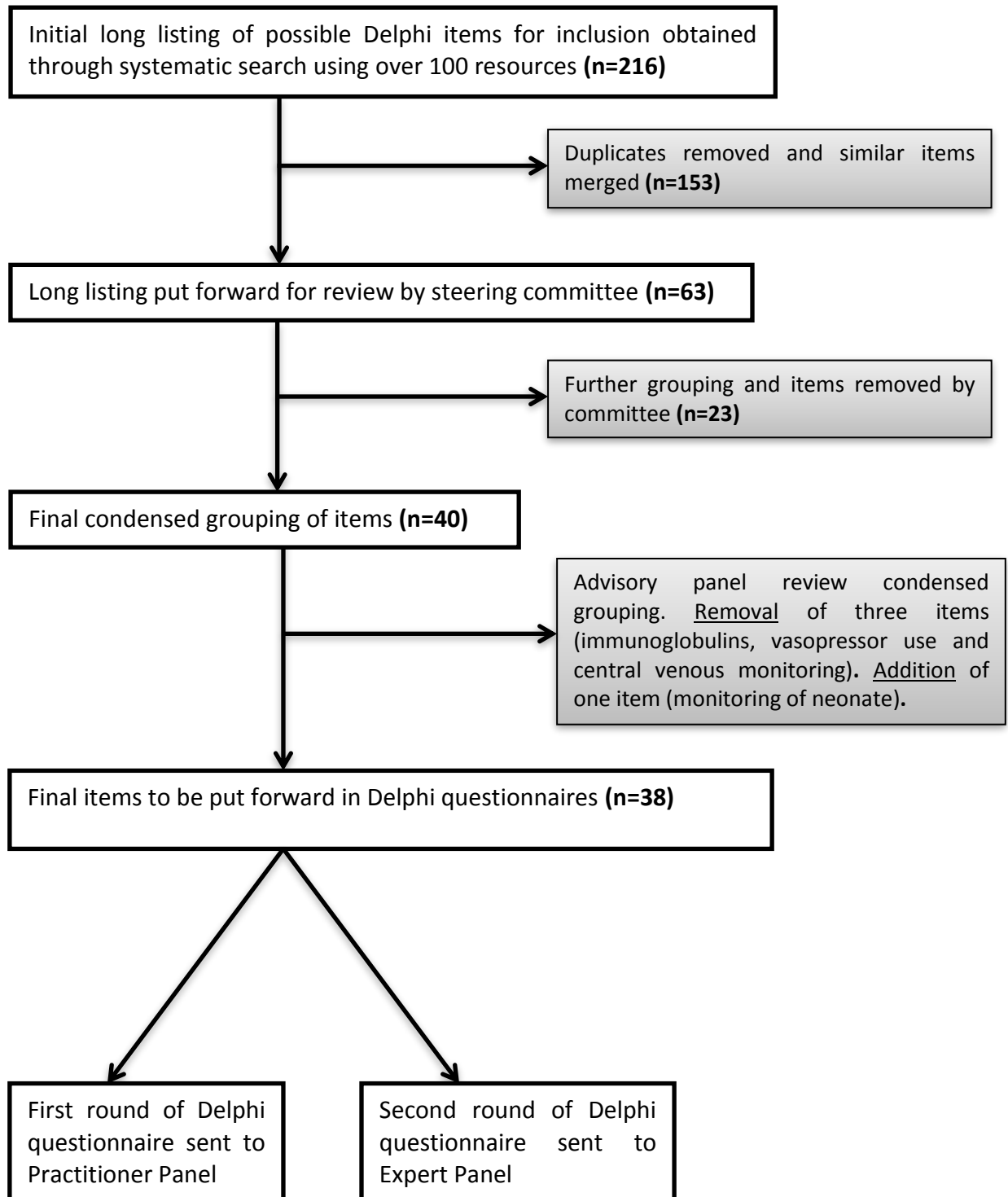
This long-list of potential items was shared with an advisory panel of experts in global maternal health, including doctors and clinical academics working in intensive care, neonatology and obstetrics. The advisory panel's role was to provide guidance on the components put forward for consideration. It was felt this was necessary prior to sending the questionnaire out to ensure the most appropriate resources were used and no items were omitted.

Comments from the advisory panel were received, with useful edits and changes to be made. They advised to exclude three items that were seen to be inappropriate and definitely unfeasible to be included in an LMIC bundle. These included: the use of intravenous immunoglobulin (which is shown to have an immunomodulatory effect) due to realistic lack of availability in low resource settings<sup>8,79,136</sup>. In addition, the use of vasopressors was excluded (for example norepinephrine and oral midodrine) which again is unlikely to be available in a low resource setting<sup>3,18,23,52,59,61,69,74,120–123,135</sup>. Central venous monitoring (to aim for central venous oxygen saturations of >70% and to monitor haemodynamic signs such as cardiac output and central venous pressure) was also excluded due to limited availability of level three care (equivalent to receiving treatment in an intensive care unit)<sup>14,69,74,80,135,136</sup>. The advisory panel also advised monitoring of the neonate to be considered as an extra monitoring point.

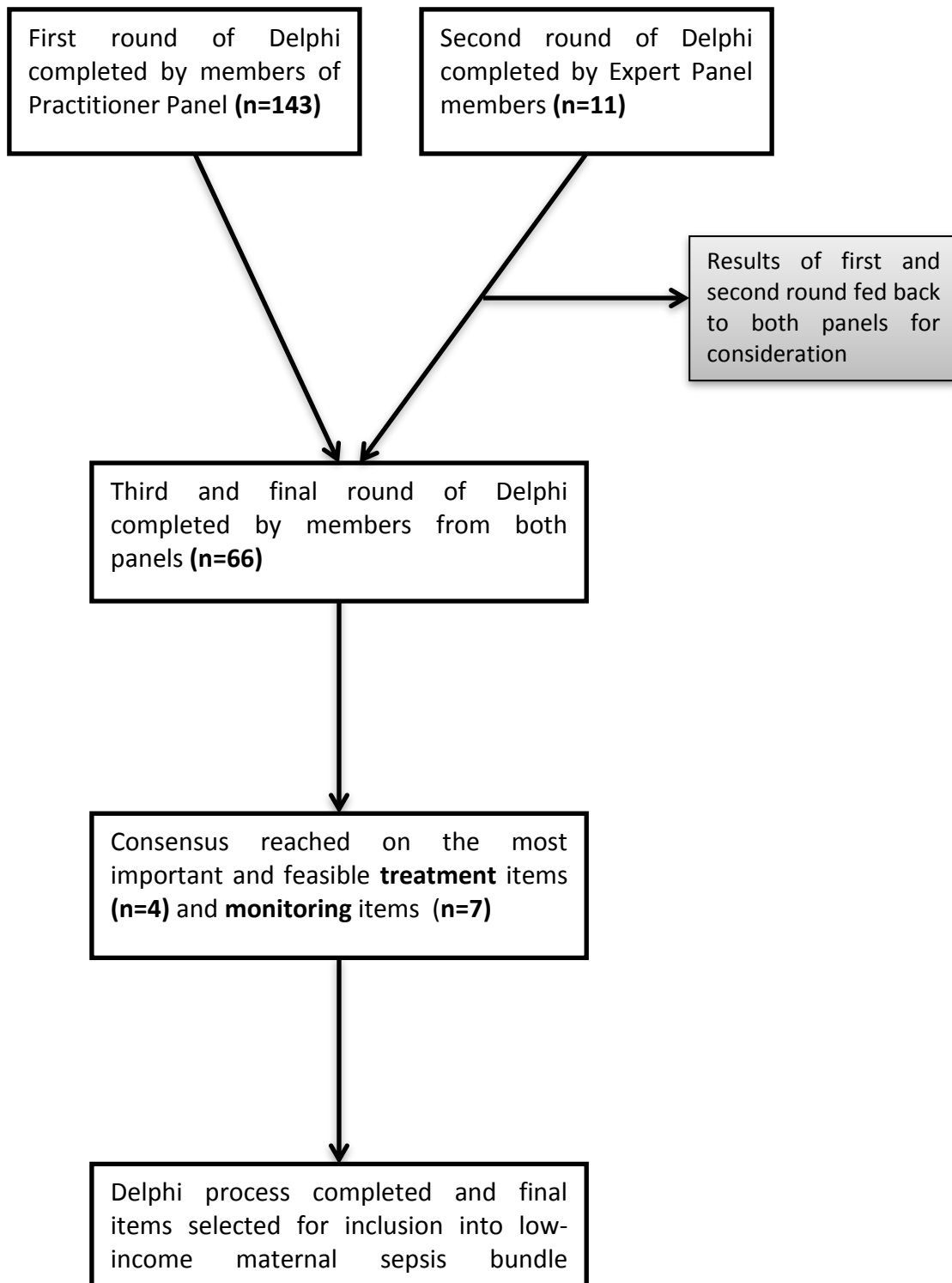
A final list of items was created and formed into questions to be put forward to stakeholders in rounds 1 and 2. Figure 5 outlines the process from selection of initial items to the first two

rounds of the Delphi process. Figure 6 shows the remainder of the process culminating in consensus being reached on the final components.





**Figure 5:** Flowchart showing selection of bundle items using Delphi method



**Figure 6:** Flowchart showing the process of the three Delphi rounds

## **Round One**

In December 2015, an online questionnaire was produced (using Smart Survey<sup>TM138</sup>). The survey was distributed to healthcare workers based in low and lower-middle income countries; or practitioners in high-income countries who have had experience and have worked in low-income settings. We used the World Bank classification<sup>26</sup> to identify the countries that were classed as low and lower-middle income. A large cohort of contacts was gained through professional networks, literature reviews and online searches. The questionnaire was cascaded via email to hundreds of eligible contacts and many of the practitioners from South America and Malawi were given the link to the survey via colleagues and so the network grew. In total, 386 emails were sent, however this is a rough estimate and it is difficult to know the exact number given the snow-balling of the email to relevant participants who may have been interested. An information sheet was attached to the email to provide additional information about our project (appendix 2) and an email address was also provided so that respondents could ask questions if required. Reminder emails were sent every four weeks and a deadline was given for the end of February 2016 (two months after the survey opened) to encourage participants to respond in a timely manner.

We asked our practitioner panel introductory questions to ascertain their background and range of practice. We then asked four main questions and invited them to offer ideas in free text responses throughout the questionnaire. The questions asked respondents to give a score for each included possible item (using a Likert scale out of 4 or 5) in terms of both importance and feasibility in both a health centre and hospital setting, for the immediate

management of maternal sepsis (within 3 hours of admission). The full questionnaire can be found in appendix 3. Respondents were from a number of cadres including Obstetricians, Clinical Officers, Nurses, Midwives, Nurse-Midwives and Scientists and Researchers. Implicit consent to participation was considered upon taking the survey. There was no incentive offered to participants completing the survey.

### **Round Two**

Round two commenced in February 2016. For our second round, we hand-selected a group of internationally renowned experts within the field of global health, sepsis and obstetrics and gynaecology. The steering committee suggested international authorities in these fields and selected the most recognised, widely published academics. An email was sent to all experts, outlining the project and progress thus far and asking if they would like to be part of the Delphi process. We did not reveal the results from round one, as we did not want to introduce any response bias or lead the expert panel's answers in any way. In addition to the Likert scale questions, we took into consideration the comments received from the expert panel and compared them with those from the practitioner panel.

Immediately after completion of round two, the committee attended a meeting at the World Health Organization (WHO) in Geneva, Switzerland, with the Maternal Sepsis Working Group (now called the Global Maternal and Neonatal Sepsis Working Initiative). At this meeting, discussions took place regarding the future of maternal sepsis research, especially in developing countries. In order to gain expert opinion on the progress and preliminary results

of the Delphi thus far, opinions were sought from members of the WHO team. There was general agreement on the initial elements to be included within the bundle. There was no formal voting or consensus forming activity undertaken here, however expert feedback and reassurance was obtained which was useful for the remainder of the Delphi process. It did not influence the answers or responses obtained from any of the three rounds.

### **Round Three**

Following completion of the first two rounds, a report was produced outlining the answers to the Likert scale questions in the form of a 100% stacked bar chart. Bar charts were produced for importance and feasibility (in both a health centre and hospital setting) for both the practitioner and expert panels (figures 9-14 and 17 & 18). In addition, scatter plots were created to outline the relationship between importance and feasibility for the practitioner panel (figures 15 & 16 and 19 & 20). Tables showing the statistically most important elements were also provided, showing the rank given to the top 5 treatment and top 7 monitoring items, in addition to the mean and standard deviations derived for each item (tables 8 and 9).

This information was provided to all participants from the first and second rounds to ensure they were able to provide informed answers to the final round. The third round was circulated in March 2016 and asked participants if they agreed with the final items presented and invited them to offer ideas on additional or missing items. A copy of the questionnaire distributed in round three can be found in appendix 4.

## RESULTS

Overall, 154 stakeholders from 34 countries offered their opinions through online questionnaires over three rounds of our modified Delphi study. Consensus on the final aspects of the bundle was reached following the second round and was confirmed in the third and final round.

### Practitioner Panel Round

In total, 143 final responses were received in the practitioner panel round from a number of different cadres. Demographics included obstetricians (57% n=81), clinical officers (19% n=27), nurses/midwives/nurse-midwives (8% n=12) as well as general doctors (5% n=7). 6% (n=8) of recipients classified themselves as “other” (such as: paediatrician, infectious disease specialist, matron) and the remaining responses were from scientists/researchers (4% n=6) or those who worked in administration or managerial roles (1% n=2).

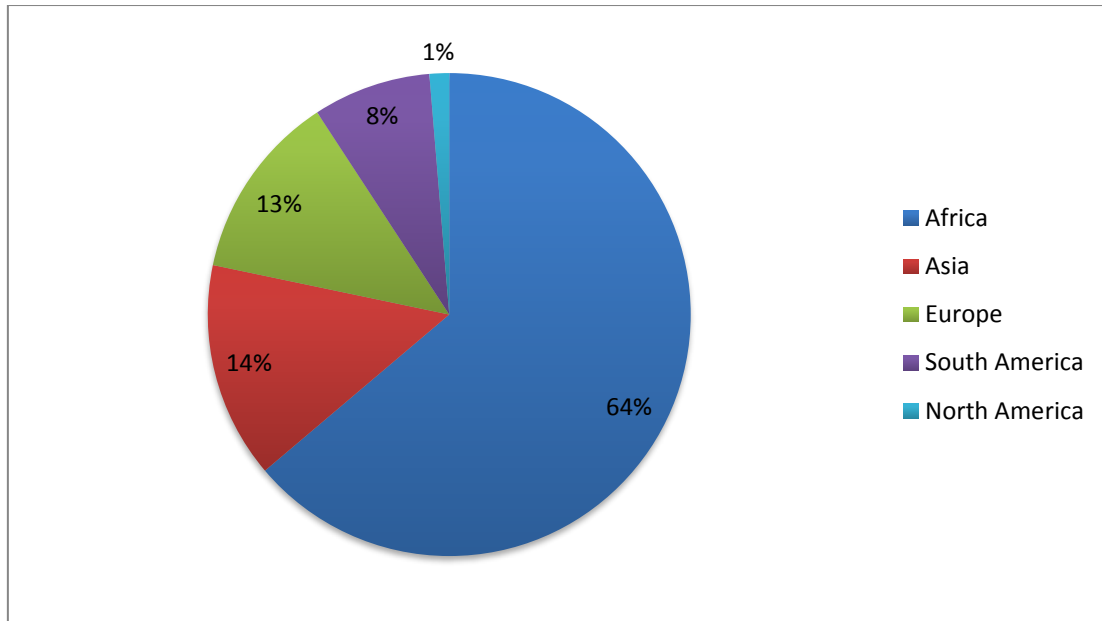
Respondents were from over 34 different low and lower-middle countries in Europe, Asia, Africa, North and South America, showing good overall global coverage. Many stakeholders who responded had worked in more than one LMIC and had noted their answers were based on their experiences in a number of countries, including LMIC. Figure 7 shows the proportion of responses from each continent. Our results show that 63.8% of responses were from Africa - with just under a third of total responses (30.3%) coming from Malawi. Asia represented 14.5% of responses incorporating countries such as Pakistan, India, Sri Lanka and others. The remainder of the results were from Europe (including the UK and Belgium -

12.5%), South America (including LMICs such as Honduras, Bolivia, Nicaragua and El Salvador - 7.9%) and North America (USA & Haiti - 1.3%).

Most practitioners in this round stated that they worked in a tertiary centre (with specialist services) (45.5% n=65) or district general hospital (38.5% n=55). A small percentage worked in a health centre (3.5% n=5) or community setting (4.9% n=7) and there were a number of respondents who identified as “other” (7.6% n=11). Those in the “other” category were either retired, worked in a university or an NGO or in management (figure 8).

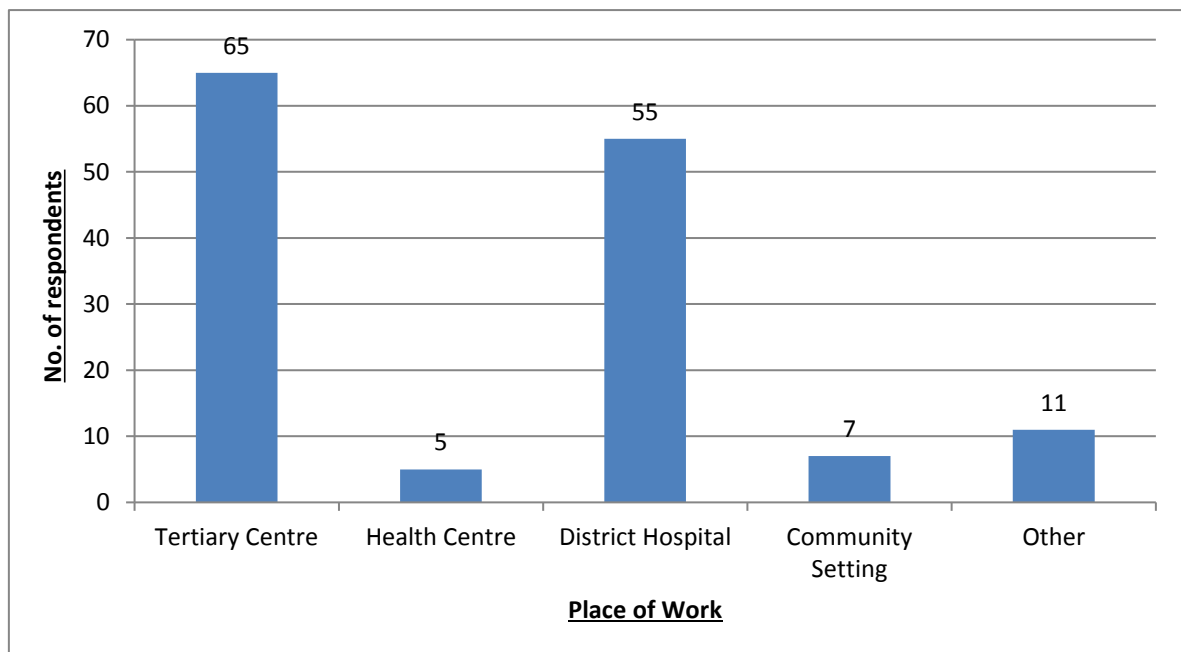
When asked if they had managed a patient with maternal sepsis in the last six months, 76.9% (n=110) of stakeholders responded “yes”, suggesting the majority of the practitioner panel have had recent, relevant clinical experience.

Following the initial questions, practitioners were asked to give a score on the importance and feasibility of the possible bundle items using a Likert scale. Firstly, they were asked to select a score between 1 and 5 for the importance of all 38 items (13 treatment items and 25 monitoring items), where 1 = very un-important and 5 = very important. They were then asked to assign a score between 1 and 4 to the feasibility of all the items, where 1 = definitely un-feasible and 4 = definitely feasible (see appendix 2).



**Figure 7:** Pie chart showing proportion of Round 1 respondents from different continents





**Figure 8:** Bar chart showing the places of work of Round 1 respondents

The scores given for the treatment items and monitoring items are shown in figures 9 and 10, respectively. Data is presented as 100% stacked bar charts with colours corresponding to the score given. The percentage highlighted indicates the proportion of respondents giving a score of 5/5 – “very important”.

The results for the feasibility of both treatment and monitoring items in a health centre and hospital setting are depicted in figures 11-14. For the purpose of this study, a health centre is a facility which aims to provide basic emergency obstetric care (BEmOC) which includes a number of interventions such as the administration of antibiotics or uterotonic drugs, manual removal of the placenta and retained products and basic neonatal resuscitation care<sup>139</sup>. Vaginal deliveries, including assistance with vacuum<sup>139</sup>, would usually take place, as well as routine antenatal and post-natal care but there is no recourse to caesarean section. There may be non-physician clinicians present as well as nurses and midwives; however it is unlikely there will be any doctors working at this sort of facility.

Again, data is presented as 100% stacked bar chart with colours corresponding to the score given. The percentage highlighted indicates the proportion of respondents giving a score of 4/4 - “definitely feasible”.

Figure 9 demonstrates the 5 most important **treatment** items, as selected by the practitioner panel. The most important item was the administration of early antibiotics, with 96.5% of practitioners giving it a score of 5 from 5 (very important). The second most important item was venous access (91.6% scoring 5) followed by administration of

intravenous fluids (82.5% giving a score of 5). This was followed by the correct identification of the source of infection (69.9% scoring 5) and finally transport to the most appropriate location (62.9% giving a score of 5).

In terms of feasibility, practitioners highlighted the most feasible **treatment** items in a health centre as shown in figure 11. Giving an antipyretic medication was seen as most feasible, with 72% of practitioners giving a score of 4 from 4 (definitely feasible). Obtaining venous access and administration of intravenous fluids was also deemed as feasible (72% and 71.3% respectively). 65.7% of practitioners also gave correct positioning of the patient and administration of antibiotics a score of 4.

These top five treatment items were also deemed as the most feasible in a hospital setting, although in a slightly different order with venous access seen as the most feasible item in a hospital and antipyretics as the fifth most feasible item (figure 13).

Moving on to the most important **monitoring** items, it was found that the measurement of blood pressure was seen as the most important with 90.2% of practitioners giving a score of 5 from 5 (very important) as shown in figure 10. 89.5% of practitioners gave measurement of respiratory rate and heart rate a score of 5 along with 82.5% for the measurement of urine output. Assessment of conscious level was also seen as very important with 81.1% of practitioners giving it a score of 5. 75.5% of practitioners also gave measurement of temperature the very important score.

In addition to these top five items, monitoring of the baby, measurement of white cell count and oxygen saturation also scored highly in terms of importance.

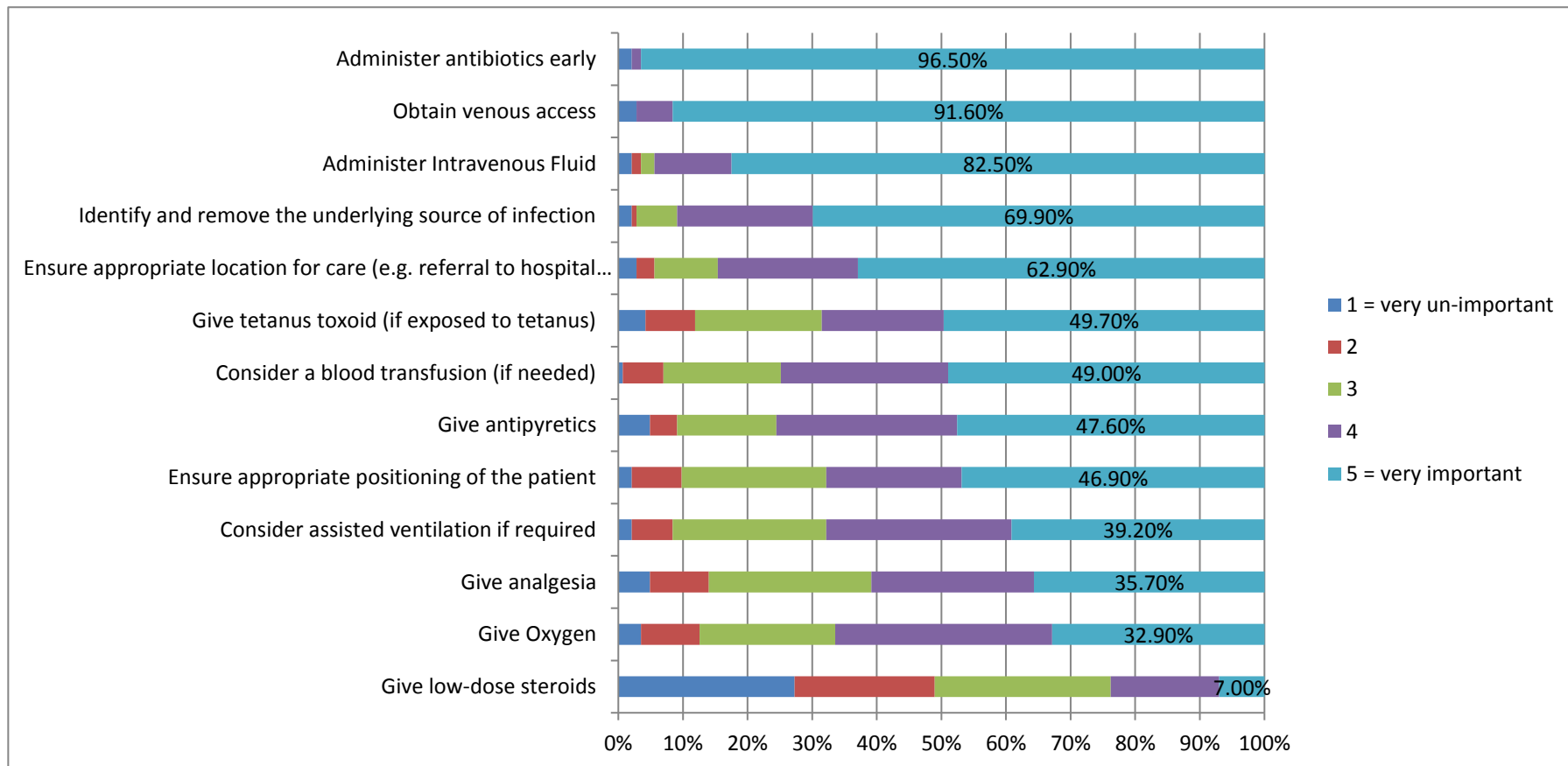
Looking at the feasibility of **monitoring** items, there were some differences seen with the ranking between a health centre and hospital setting. Figure 12 shows the top five most feasible items in a health centre to be measurement of blood pressure, with 79.7% of practitioners giving it a score of 4 (definitely feasible), along with the measurement of temperature. 79% of practitioners gave measurement of respiratory rate and heart rate a score of 4 and 69.9% gave this score to assessment of conscious level. Finally, 57.3% of practitioners gave malaria testing a score of 4.

In a hospital setting, measurement of urine output was seen as more feasible than malaria testing, in terms of its ranking amongst all the monitoring items (figure 14).

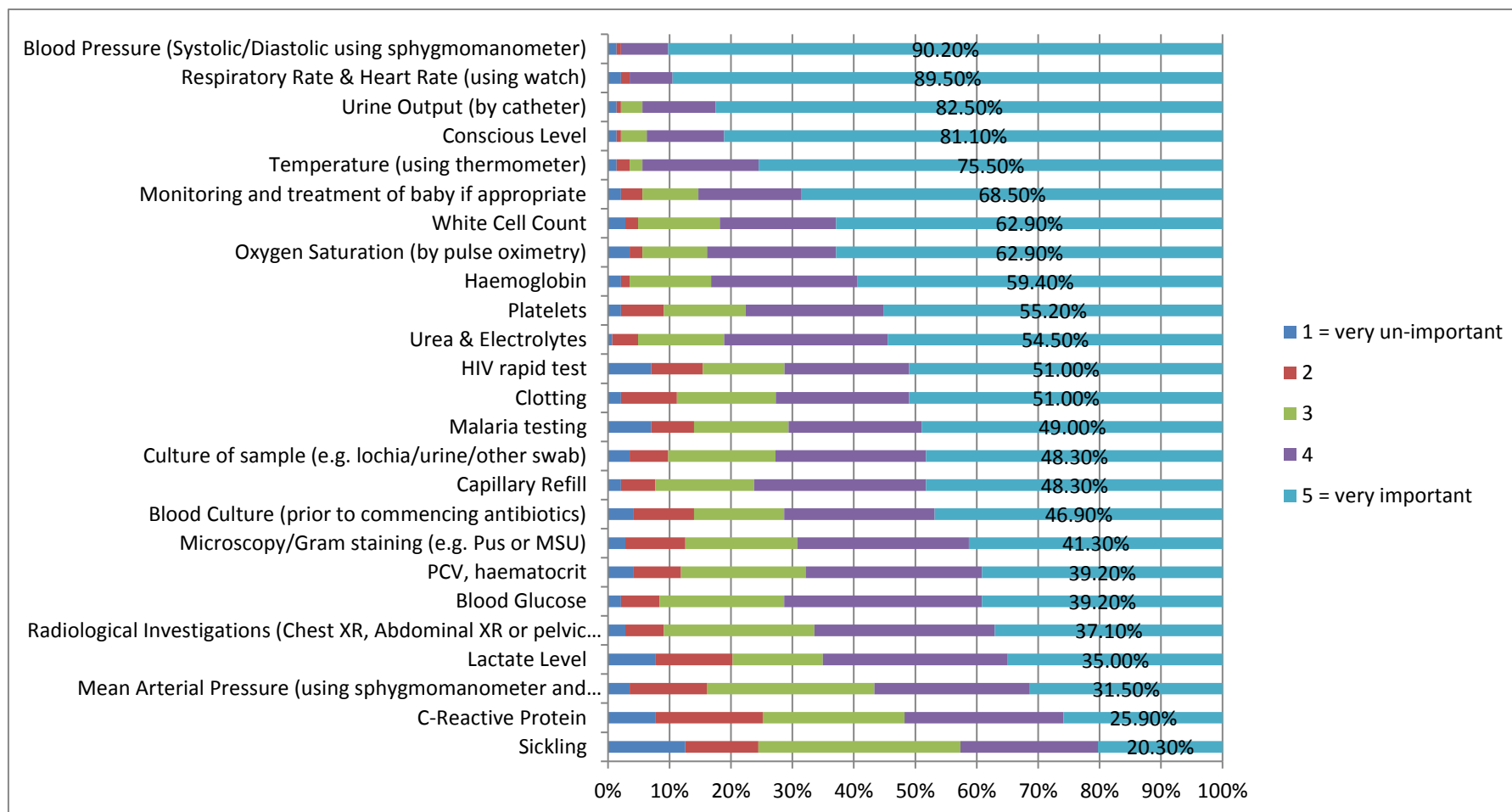
We looked at the relationship between importance and feasibility for both treatment items (figure 15) and monitoring items (figure 16) in both a health centre and hospital setting. These scatter plots graphically represent the percentage of respondents who scored an item as “definitely feasible” against the percentage scoring the item as “very important”.

It is interesting to see there are three main **treatment** items that are seen as both “very important” and “definitely feasible” – obtaining venous access, administering antibiotics and IV fluids. A number of items that were seen as very important were also reasonably feasible, including ensuring appropriate location for care and appropriate positioning (figure 15).

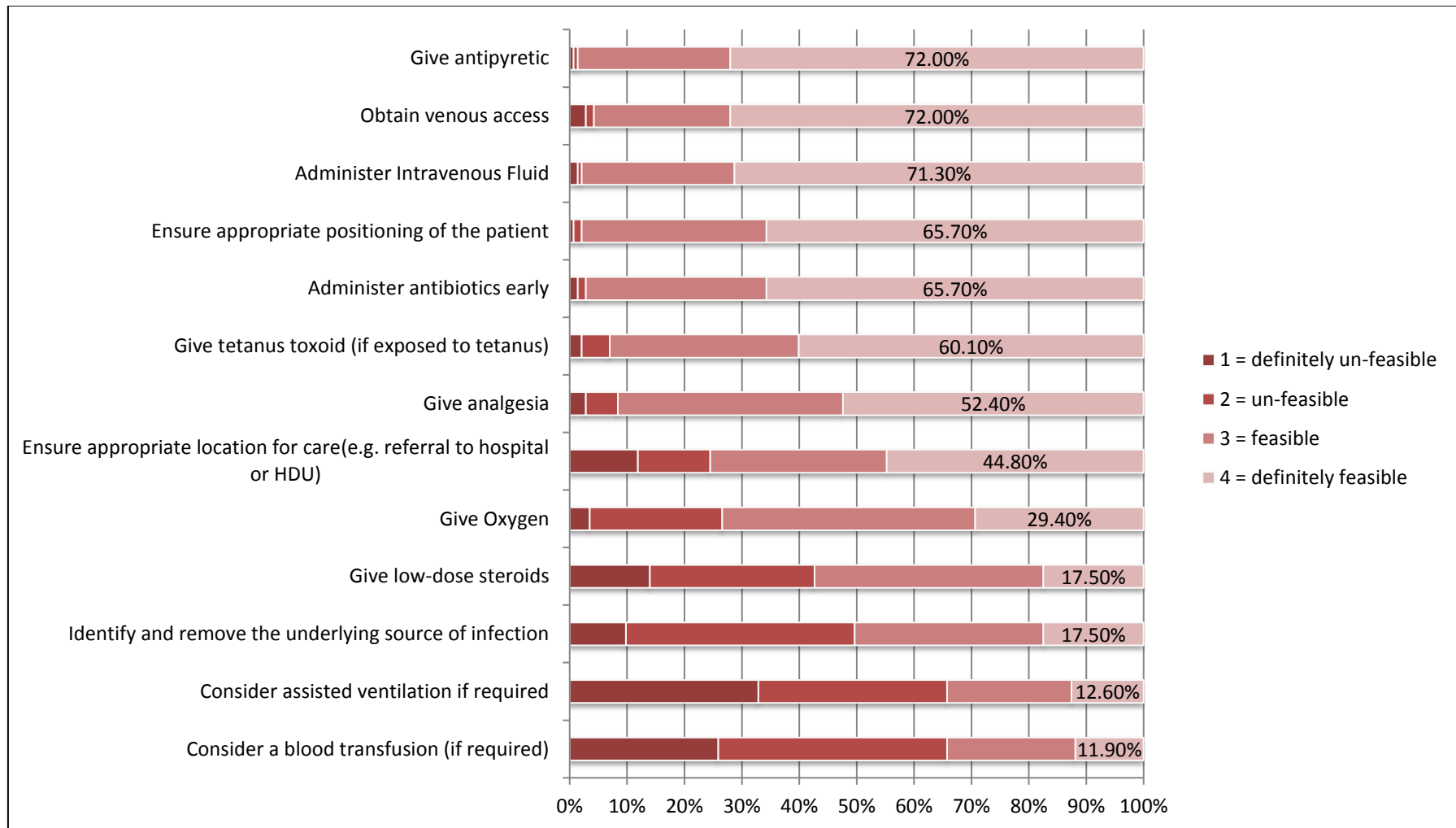
In terms of **monitoring**, there is a clear correlation demonstrated between importance and feasibility in five items – measurement of blood pressure, measurement of respiratory rate and heart rate, urine output, conscious level and measurement of temperature. It is reassuring that the most important and feasible treatment and monitoring items are interventions that are practical and possible in a lower income setting.



**Figure 9:** Results from the first round Delphi survey regarding the importance of treatment items using a Likert scale

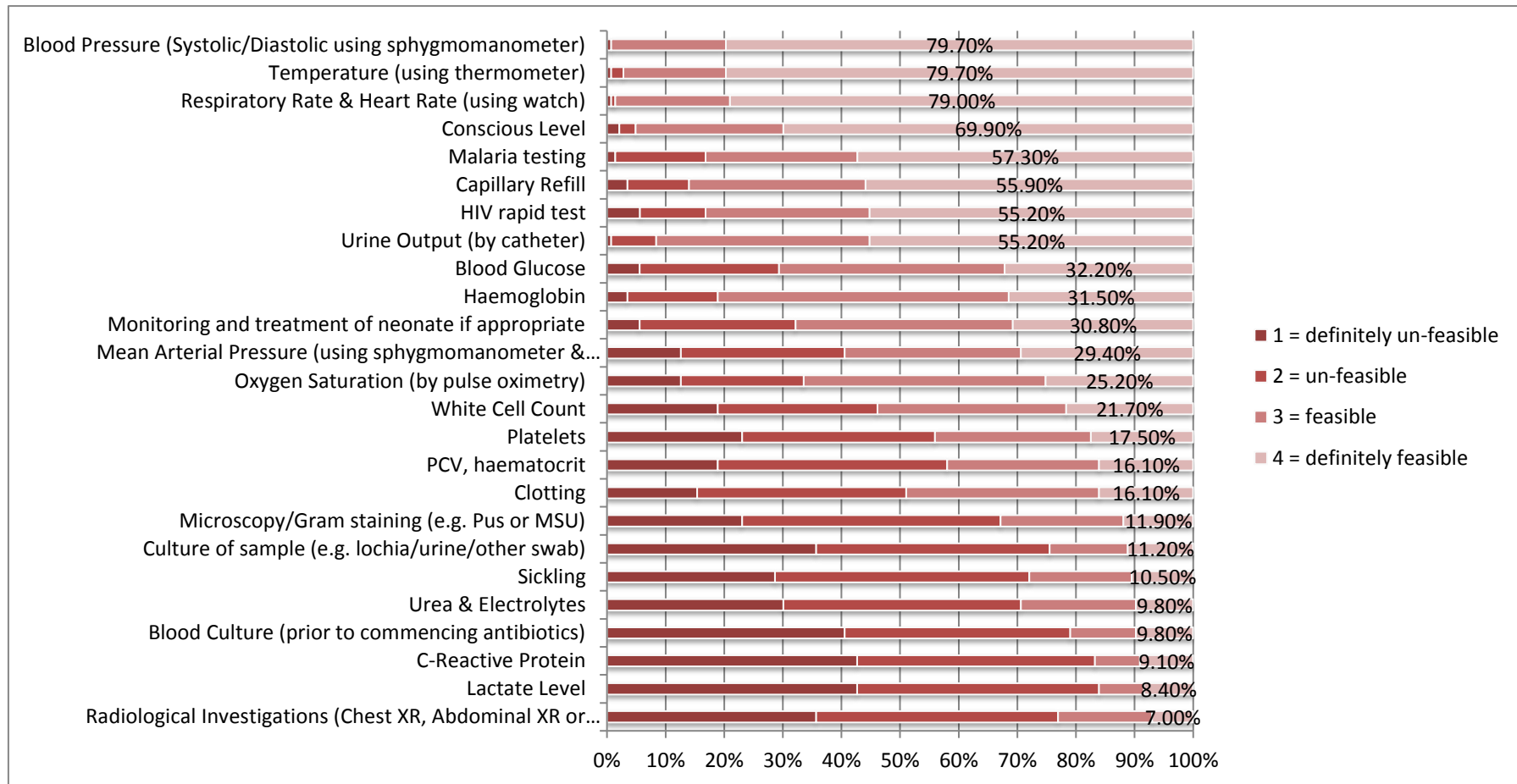


**Figure 10:** Results from the first round Delphi survey regarding the importance of monitoring items using a Likert scale

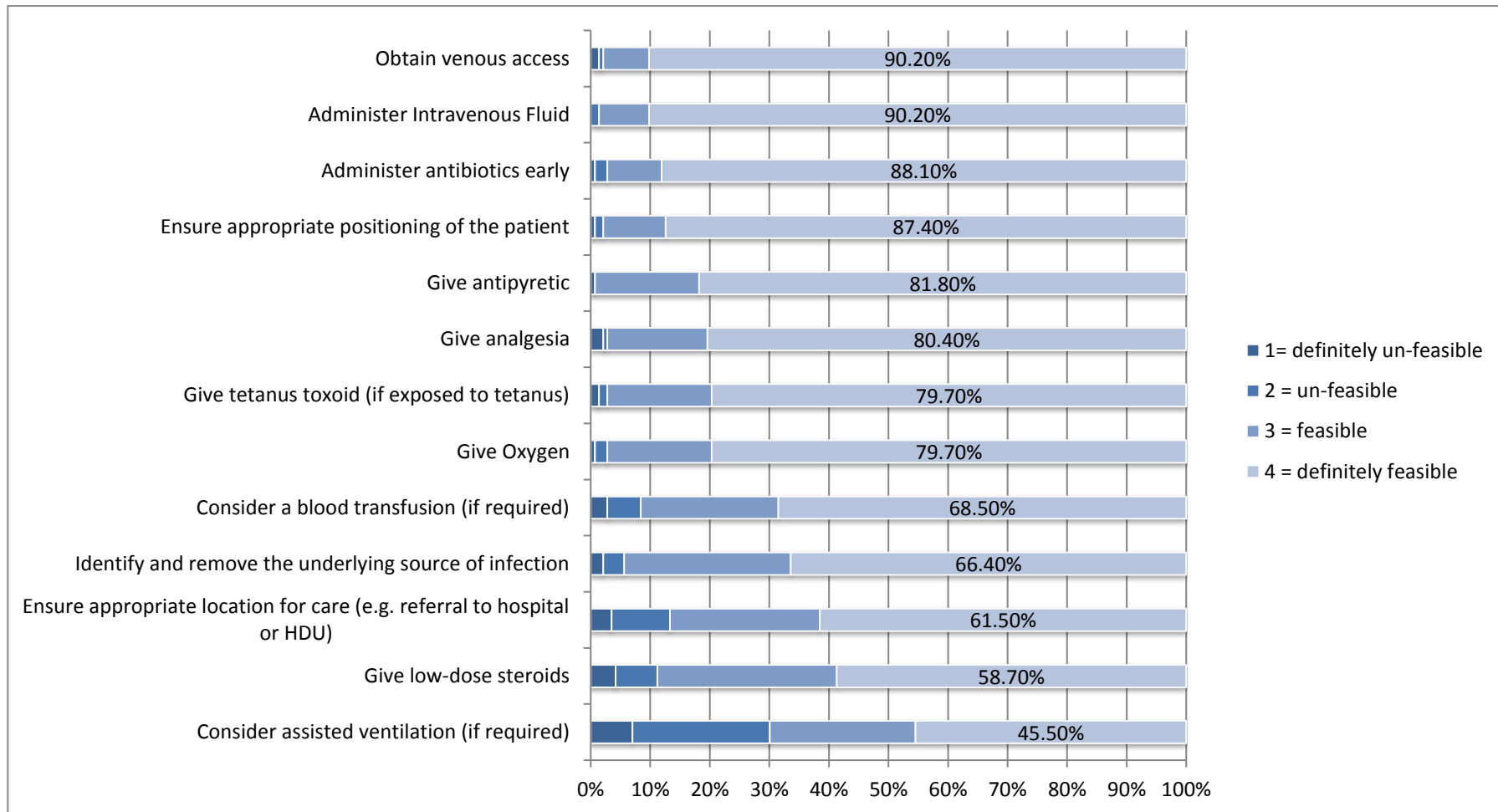


**Figure 11:** Results from the first round Delphi survey regarding the feasibility of treatment items in a health centre setting using a Likert score out of 4

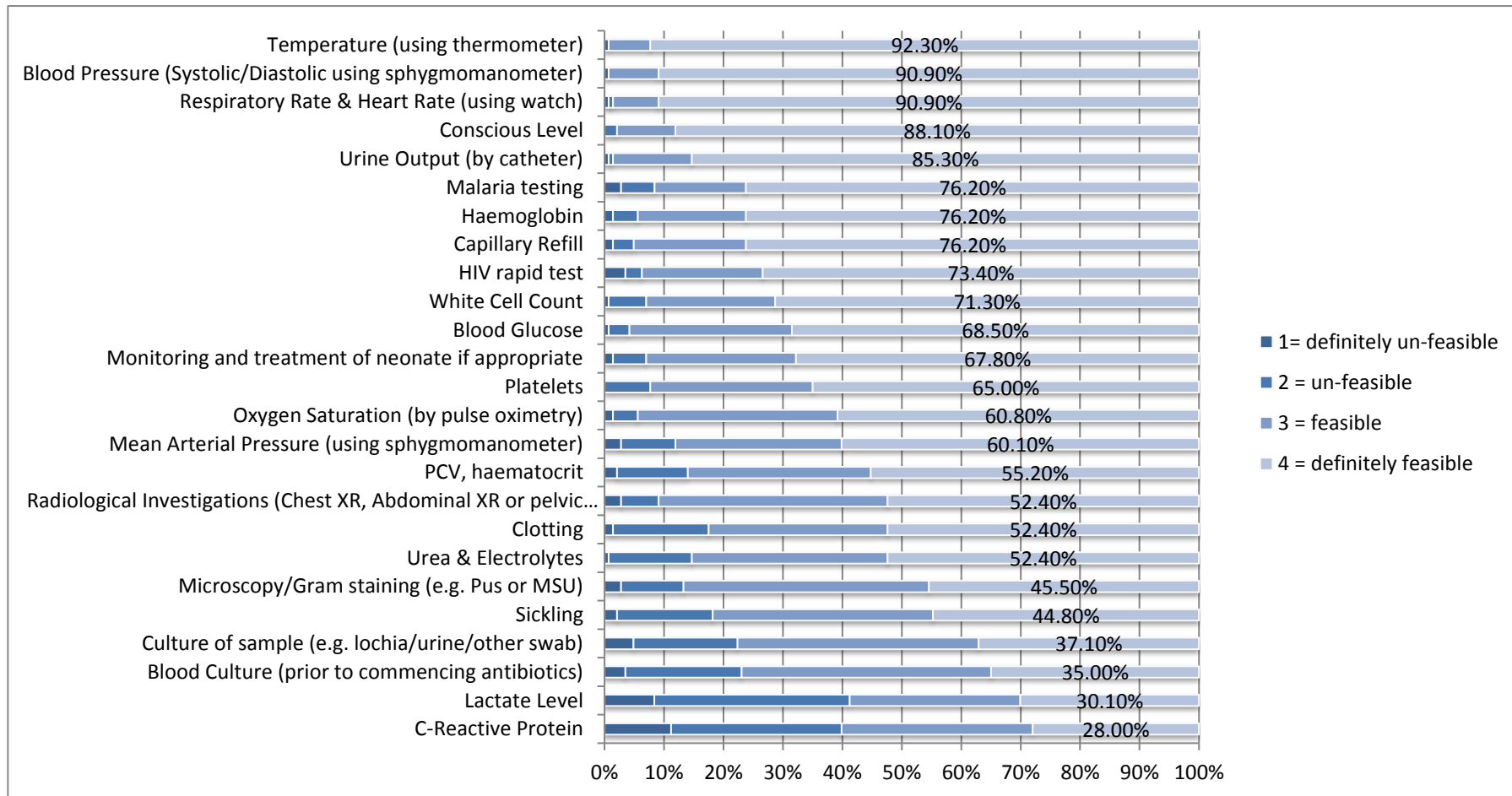




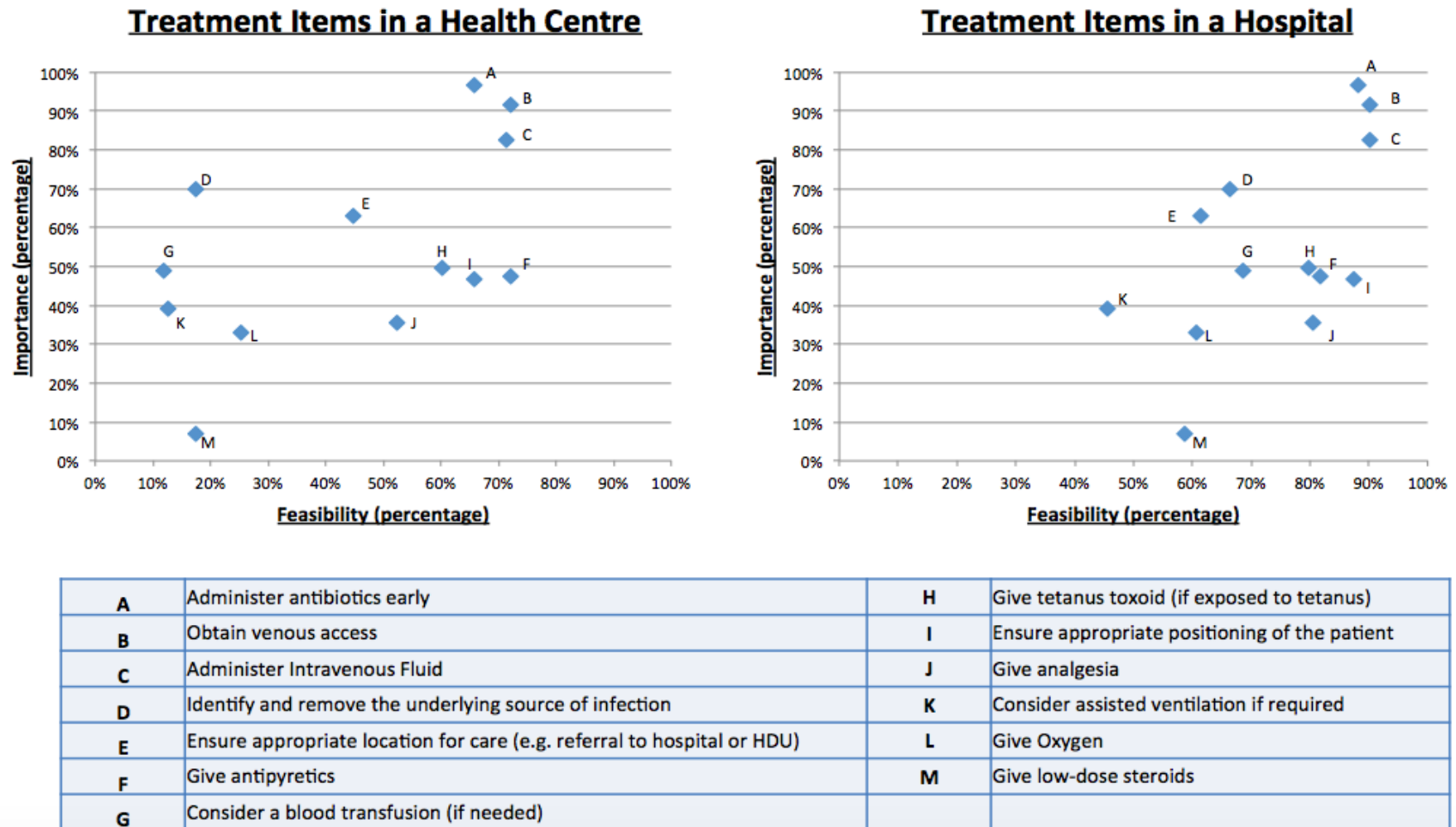
**Figure 12:** Results from the first round Delphi survey regarding the feasibility of monitoring items in a health centre setting using a Likert score out of 4



**Figure 13:** Results from the first round Delphi survey regarding the feasibility of treatment items in a hospital using a Likert score out of 4

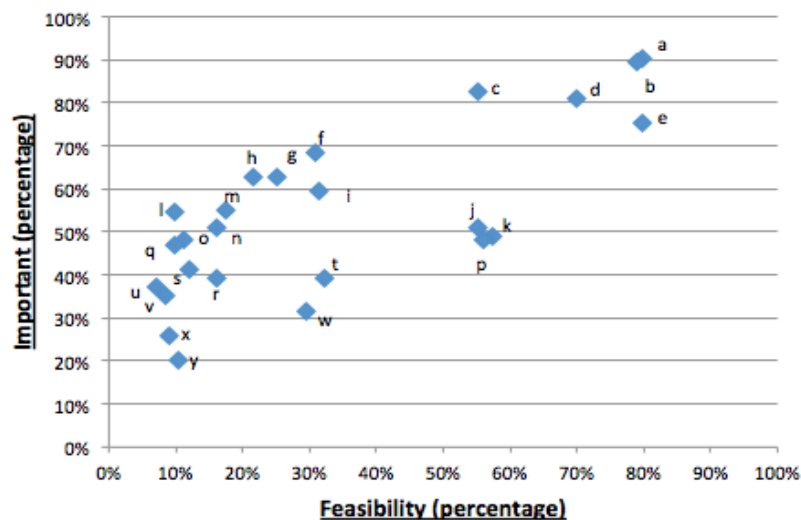


**Figure 14:** Results from the first round Delphi survey regarding the feasibility of monitoring items in a hospital using a Likert score out of 4

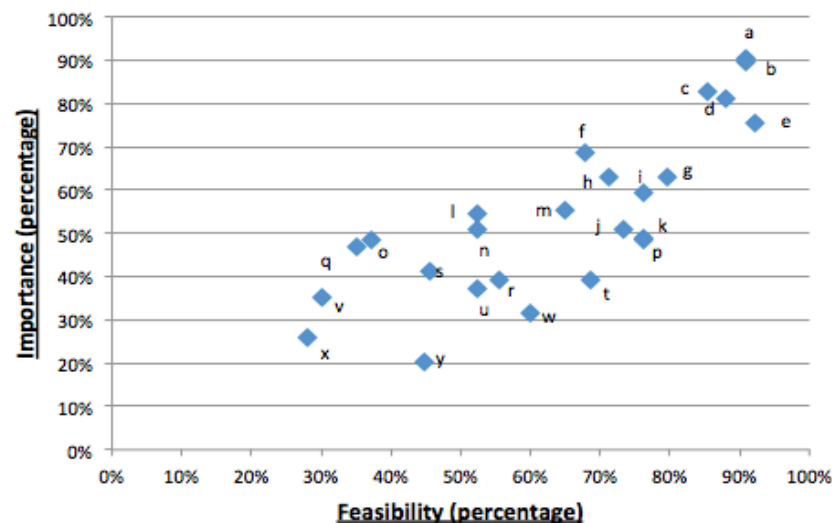


**Figure 15:** Scatter plots showing the relationship between importance and feasibility of treatment items in a hospital and health centre

### Monitoring Items in a Health Centre



### Monitoring Items in a Hospital



a	Blood Pressure (using sphygmomanometer)	j	HIV rapid test	s	Microscopy/Gram staining (e.g. Pus or MSU)
b	Respiratory Rate & Heart Rate (using watch)	k	Malaria testing	t	Blood Glucose
c	Urine Output (by catheter)	l	Urea & Electrolytes	u	Radiological Investigations (e.g. XR or USS)
d	Conscious Level	m	Platelets	v	Lactate Level
e	Temperature (using thermometer)	n	Clotting	w	Mean Arterial Pressure
f	Monitoring and treatment of baby if appropriate	o	Culture of sample (e.g. lochia/urine)	x	C-Reactive Protein
g	Oxygen Saturation (by pulse oximetry)	p	Capillary Refill	y	Sickling
h	White Cell Count	q	Blood Culture (prior to antibiotics)		
i	Haemoglobin	r	PCV, haematocrit		

Figure 16: Scatter plots showing the relationship between importance and feasibility of monitoring items in a hospital and health centre

### **Expert Panel Round**

In order to compare results, we analysed the answers from the expert panel identically to the practitioner panel.

We received 11 responses from our selected expert panel. Experts were from a variety of backgrounds with 63.6% (n=7) of responses from obstetricians, 18.2% (n=2) from other specialist doctors (infectious diseases & paediatrics), 9.1% (n=1) from intensive care/anaesthetic doctors and 9.1% (n=1) from scientist/researchers. Respondents were mainly based in higher income countries such as the UK and Canada, but had experience in countries such as Malawi, Uganda, Nigeria, Kenya, Ghana, India, Pakistan, Bangladesh and Thailand. Although members of the expert panel may not be currently practicing a low or lower-middle income country, they had all had experience in implementation of similar projects and other global health projects, pertaining to sepsis and maternal health.

As members of the expert panel were not working in low-income settings, only their responses regarding each item's importance were analysed.

It was found that the top five most important **treatment** items matched those of the practitioner panel exactly, with administration of antibiotics, venous access, administration of fluids, identifying the underlying source of infection and appropriate location of the patient being selected, as shown in figure 17.

In terms of monitoring, the top five most important **monitoring** items, that experts scored 5 out of 5 included assessment of conscious level (81.8%) and measurement of respiratory rate and heart rate (81.8%), as shown in figure 18. 63.6% of experts gave the following 3 items a score of 5: monitoring of baby, measurement of urine output and measurement of blood pressure.

Measurement of temperature and oxygen saturation also scored highly for importance. Although the order is slightly different, the top seven items were exactly the same for both the practitioner and expert panel. This again indicates agreement between the panels in terms of the most important treatment and monitoring factors.

When looking at the relationship between feasibility and importance, there were some interesting conclusions. In an identical pattern to the practitioner panel, the expert panel felt that the top three most important and feasible **treatment** items included administration of antibiotics, venous access and administration of IV fluids in both a health centre and hospital setting. The scatter plot in figure 19 also shows a number of other items that were deemed both important and feasible including appropriate location of the patient, giving an antipyretic and giving tetanus toxoid if required.

In terms of **monitoring**, the most feasible and important items found by the expert panel were also found to be exactly as the practitioner panel had recommended with the top items for a health centre being: measurement of blood pressure, measurement of respiratory rate and heart rate, assessment of conscious level and measurement of

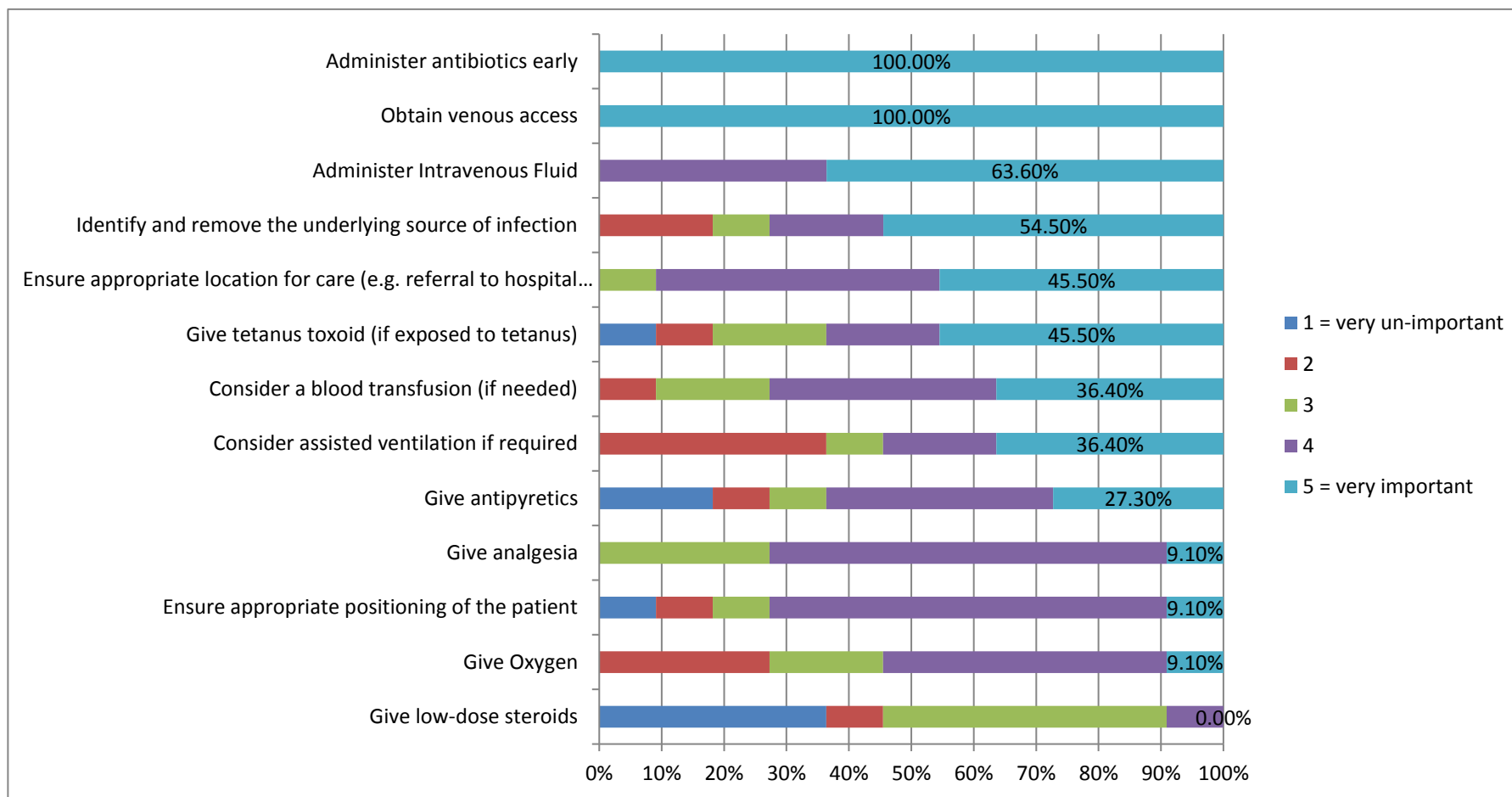
temperature. Figure 20 also shows that, in a hospital setting, the measurement of urine output was also seen to be a very important and feasible item. These five items match the pattern of the most feasible and important items selected by the practitioner panel, indicating general consensus at the end of round two.

We created two tables (table 8 & 9) showing with the ranking of the most important treatment and monitoring elements, according to the mean and standard deviation score applied to each item, by both the practitioner panel and the expert panel.

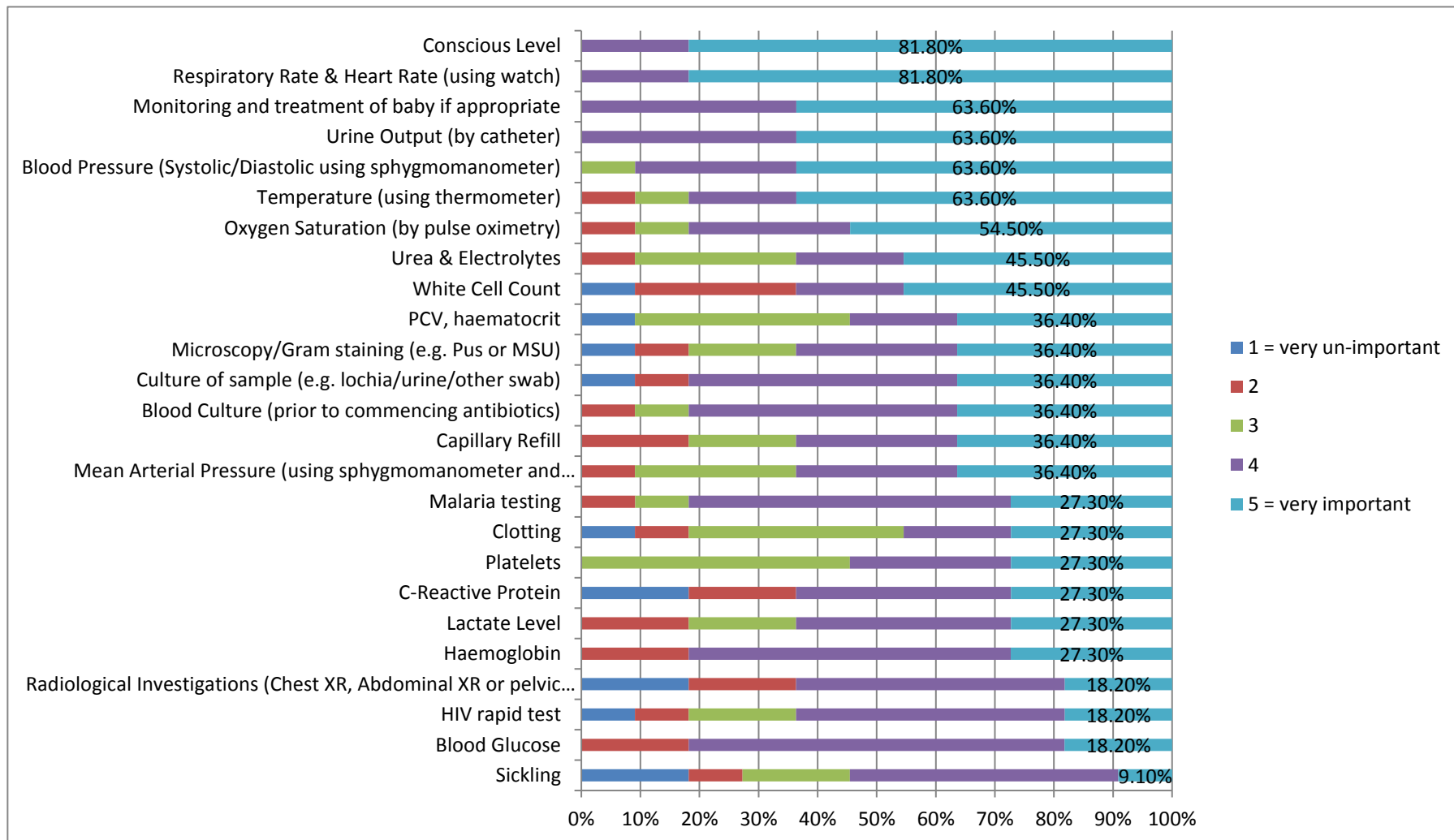
Table 8 shows that both the practitioner and expert panel have ranked these same items as the top five most important **treatment** items. Similarly, table 9 shows statistically, both panels ranked the same top seven **monitoring** items, although in a slightly different order.

These tables, in addition to the graphs, suggest that general consensus between both panels had been confirmed at the end of round two. However, a final round was required to confirm these findings, whereby members from both panels received detail feedback on the results thus far and were asked their final opinion in the form of a final questionnaire (see appendix 4).

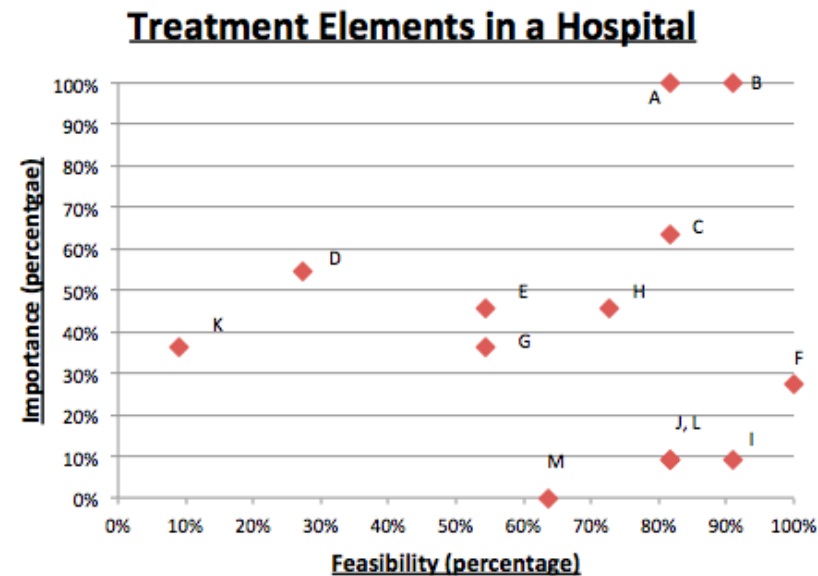
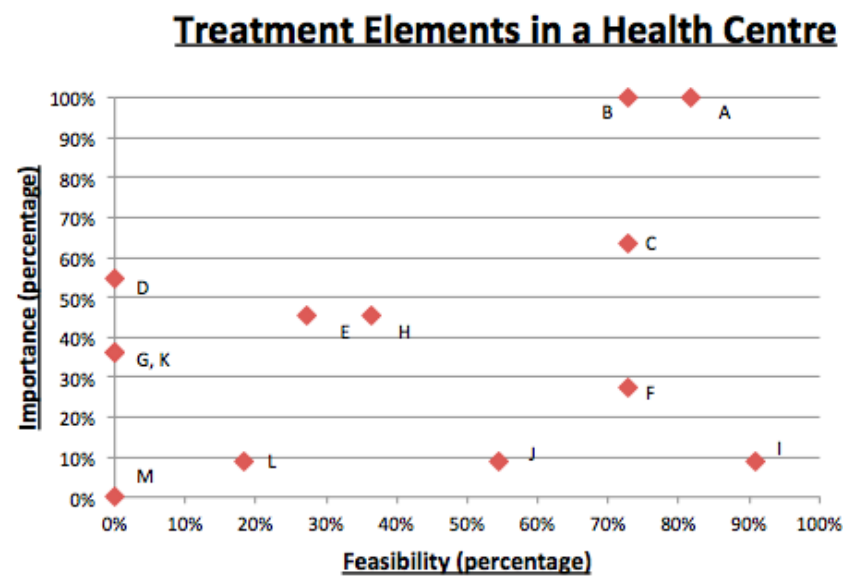




**Figure 17:** Results from the second round Delphi survey regarding the importance of treatment items using a Likert scale out of 5



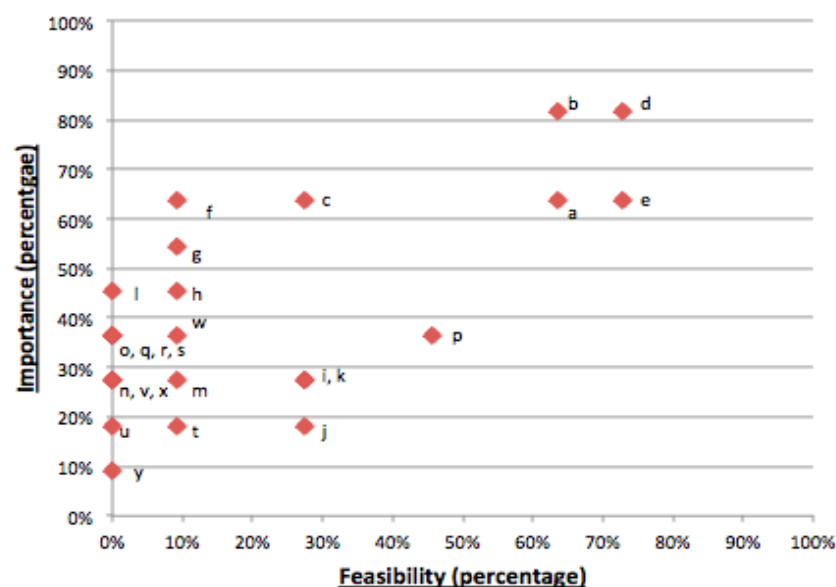
**Figure 18:** Results from the second round Delphi survey regarding the importance of monitoring items using a Likert scale out of 5



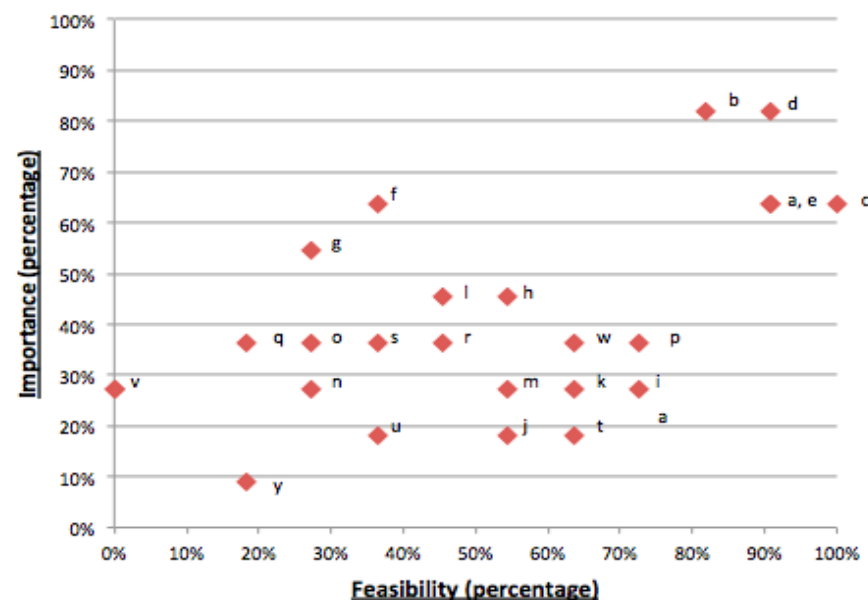
<b>A</b>	Administer antibiotics early	<b>H</b>	Give tetanus toxoid (if exposed to tetanus)
<b>B</b>	Obtain venous access	<b>I</b>	Ensure appropriate positioning of the patient
<b>C</b>	Administer Intravenous Fluid	<b>J</b>	Give analgesia
<b>D</b>	Identify and remove the underlying source of infection	<b>K</b>	Consider assisted ventilation if required
<b>E</b>	Ensure appropriate location for care (e.g. referral to hospital or HDU)	<b>L</b>	Give Oxygen
<b>F</b>	Give antipyretics	<b>M</b>	Give low-dose steroids
<b>G</b>	Consider a blood transfusion (if needed)		

**Figure 19:** Scatter plots showing the relationship between importance and feasibility of treatment items in round two

### Monitoring Elements in a Health Centre



### Monitoring Elements in a Hospital



a	Blood Pressure (using sphygmomanometer)	j	HIV rapid test	s	Microscopy/Gram staining (e.g. Pus or MSU)
b	Respiratory Rate & Heart Rate (using watch)	k	Malaria testing	t	Blood Glucose
c	Urine Output (by catheter)	l	Urea & Electrolytes	u	Radiological Investigations (e.g. XR or USS)
d	Conscious Level	m	Platelets	v	Lactate Level
e	Temperature (using thermometer)	n	Clotting	w	Mean Arterial Pressure
f	Monitoring and treatment of baby if appropriate	o	Culture of sample (e.g. lochia/urine)	x	C-Reactive Protein
g	Oxygen Saturation (by pulse oximetry)	p	Capillary Refill	y	Sickling
h	White Cell Count	q	Blood Culture (prior to antibiotics)		
i	Haemoglobin	r	PCV, haematocrit		

**Figure 20:** Scatter plots showing the relationship between importance and feasibility of monitoring items in round two

**Table 8:** The most important treatment items selected by both panels

<b>Practitioner Panel</b>	<b>Rank</b>	<b>Expert Panel</b>
<b>Antibiotics</b> Mean = 4.90, SD 0.58	<b>1</b>	<b>Antibiotics</b> Mean = 5.00, SD 0.00
<b>IV Access*</b> Mean = 4.83, SD 0.69	<b>2</b>	<b>IV Access*</b> Mean = 5.00, SD 0.00
<b>IV Fluids</b> Mean = 4.71, SD 0.76	<b>3</b>	<b>IV Fluids</b> Mean = 4.64, SD 0.48
<b>Source Control</b> Mean = 4.56, SD 0.82	<b>4</b>	<b>Location</b> Mean = 4.36, SD 0.64
<b>Location</b> Mean = 4.39, SD 0.97	<b>5</b>	<b>Source Control</b> Mean = 4.09, SD 1.16

\*IV access will be removed from the final ranking, as it is intrinsic to two other top ranked elements (administration of IV fluids and IV antibiotics).

**Table 9:** The most important monitoring items selected by both panels

<b>Practitioner Panel</b>	<b>Rank</b>	<b>Expert Panel</b>
<b>Blood Pressure</b> Mean = 4.85, SD 0.58	<b>1</b>	<b>Respiratory Rate &amp; Heart Rate</b> Mean = 4.82, SD 0.39
<b>Respiratory Rate &amp; Heart Rate</b> Mean = 4.80, SD 0.70	<b>2</b>	<b>Conscious Level</b> Mean = 4.82, SD 0.39
<b>Urine Output</b> Mean = 4.73, SD 0.69	<b>3</b>	<b>Urine Output</b> Mean = 4.64, SD 0.48
<b>Conscious Level</b> Mean = 4.71, SD 0.71	<b>4</b>	<b>Monitoring of Baby</b> Mean = 4.64, SD 0.48
<b>Temperature</b> Mean = 4.65, SD 0.75	<b>5</b>	<b>Blood Pressure</b> Mean = 4.55, SD 0.66
<b>Monitoring of Baby</b> Mean = 4.46, SD 0.94	<b>6</b>	<b>Temperature</b> Mean = 4.27, SD 0.96
<b>Oxygen Saturation**</b> Mean = 4.38, SD 1.00	<b>7</b>	<b>Oxygen Saturation**</b> Mean = 4.27, SD 0.96

\*\* Oxygen Saturation was ranked highly in terms of importance and following the discussion at the WHO meeting in February, it was suggested that while not always feasible, it should be carried out if the facilities are able to do so.

### **Final Round**

Upon completion of the first two rounds, we sent out a final questionnaire to all who participated, and achieved a good response rate. In total 39.9% (n=57) of practitioners from the first round and 81.8% (n=9) of experts from the second round replied, with a total of 66 responses overall.

The questions presented the final components of the maternal sepsis bundle, given the results ascertained from the first two rounds. We asked all participants if they **agree** with the final components by answering either “yes” or “no” to the presented treatment and monitoring items. We also asked if there were any further comments or if any elements should be added or removed.

Results showed that 96.5% (n=55) of practitioners agreed with the final **treatment** components selected with 2 participants disagreeing. One practitioner provided no further comment and the other practitioner expressed that “*IV fluids are not always necessary*”.

Regarding **monitoring** items, 98.2% (n=56) of the practitioner panel agreed with the final selection, with the one practitioner disagreeing and leaving no comment, as with the treatment items. The remaining 56 practitioners had no concerns. Minimal comments regarding additional bundle elements were given, and the comments that were provided suggested emphasis on early administration of antibiotics and concerns regarding feasibility of oxygen saturation (expressed by 2 practitioners).

Regarding the expert panel, 100% of the respondents (n=9) agreed that the final treatment and monitoring items were suitable and had no further comments.



## DISCUSSION

This global modified Delphi on maternal sepsis included a consultation with numerous stakeholders from the 34 low and lower-middle income countries. The results from this study have highlighted the most important and feasible items to be included within a maternal sepsis management bundle for use in these countries.

Each of the following items are key interventions that can be undertaken in most health centres and hospitals in low and lower-middle income countries. The components below were selected to be included in the final bundle: Fluids, Antibiotics, Source Control, Transport and Monitoring (for both mother and baby). These items can be grouped together with the acronym, FAST-M to assist in practitioner recall.

### **Fluids**

It is well recognised that the administration of intravenous fluids is an important part of sepsis management<sup>16,19,20,52,69,74,75,77,135,137,140</sup>. From our study, we can see that 82.5% of our practitioners and 63.6% of experts felt that fluids were “very important”. In terms of feasibility, 71.3% of practitioners felt that the administration of fluids were “definitely feasible” in a health centre compared to 90.2% in a hospital, showing in the majority of cases, practitioners would recommend the use of fluids. Other sepsis bundles recommend the use of intravenous fluids, specifically the Surviving Sepsis Campaign “Resuscitation Bundle<sup>22</sup>” and UK Sepsis Trust “Sepsis Six Bundle<sup>13</sup>”. In the literature, crystalloids are usually advised as a first line fluid, at a rate of 30ml/kg<sup>22</sup>. However, in resource-limited settings

where monitoring of the adverse effects of fluids may prove difficult, it is important to ensure safety is paramount, therefore this dosing may be inappropriate. It would be advisable to begin with a bolus of 500ml of a crystalloid fluid and reassess, increasing the fluids as required and undertaking the appropriate examination and monitoring to look for fluid overload including pulmonary oedema, with the resources available.

### **Antibiotics**

From our results, we can see the highest ranking component was the administration of antibiotics. This is ideally through the intravenous route and early on in the management plan. It is well documented that the use of IV antibiotics is associated with reduced mortality<sup>3,7,9,16,52–56,62,64,69,74,77–80,111,112,115,135–137,140</sup>. There was clear consensus between both panels as 100% of experts felt that antibiotics were “very important”, along with 96.5% of practitioners. Practitioners believed that in both a health centre and hospital setting, it would be “definitely feasible” to administer antibiotics, with a total of 65.7% and 88.2% of practitioners suggesting this, respectively. Bundles such as “Sepsis Six” advise the administration of antibiotics as early as possible, or within the first hour<sup>13</sup>. This is supported by evidence in the literature that associates the early administration of antibiotics with reduced mortality. Kumar et al undertook a retrospective cohort study over 15 years and found that there was a strong relationship between delayed antibiotic initiation and in-hospital mortality (adjusted odds ratio 1.12, 95% confidence interval 1.10-1.14 p<0.0001)<sup>114</sup>. Giving antibiotics within the first hour of documented hypotension was associated with a survival rate of 79.9% and for every hour of delay over 6 hours; there was an average

decrease in survival of 7.6%<sup>114</sup>, highlighting the incredibly important need to initiate antibiotic therapy early in sepsis management.

### **Source Control**

Early identification and removal of the source of infection can help to ensure earlier treatment and improved survival rates<sup>52,53,66,69,72,79,96,98,135–137,140</sup>. From our Delphi study, we can see that 54.5% of experts and 69.9% of practitioners felt that source control was “very important”. However, practitioners believed this was less feasible to do in a health centre setting with 17.5% selecting the “definitely feasible” option, compared to 66.4% in a hospital setting. This may be due to the need for diagnostic skills and equipment to identify the source of the infection, which may be difficult in more rural health centres. However, there are still aspects of source identification and control, which may be feasible in a health centre, including bedside testing and manual vacuum aspiration (MVA) post miscarriage. The discrepancies between what is available at both facilities highlights the need for adequate communication and transport in order to refer patients requiring more specialised care, to larger or tertiary centres.

### **Transport**

The appropriate location for care is important, as the facilities the patient initially attends may not be able to provide the appropriate care. The location of the patient can refer to transfer from a health centre to a hospital or even within a hospital to a unit that may be able to provide advanced care such as a high dependency or intensive care unit. Identifying

the correct level of care for a patient is important to ensure the correct treatment can be commenced rapidly<sup>8,9,16,24,51,52,58,65,66,69,70</sup>. 45.4% of experts and 62.9% of practitioners felt that transport was “very important” and hence one of the top rated items. In terms of feasibility, as per the other items, more practitioners felt that the appropriate location was “definitely feasible” in 61.5% of cases for hospitals and 44.8% in health centres.

There are a number of reasons to explain why practitioners may have felt this way. Studies and reviews have highlighted the challenges people in low and lower-middle income countries face when requiring transport. One of the main reasons this might be more of an issue in a health centre is due to its location. Health centres are likely to be in a more rural area or serve a smaller population. This can be a problem in terms of the time it would take to get to the hospital itself as well as the waiting time for a suitable mode of transportation to complete the journey.

A recent systematic review on emergency maternal transport in low-income countries identified this issue as one of the main themes and barriers to emergency transportation. Additionally the lack of transport options, especially in a rural area, was highlighted to be another major factor affecting transportation, as well as full vehicle occupancy being an issue. Community and cultural practices also play a part in delaying successful transportation, with problems such as drivers refusing to take patients for fear of litigation in case of death, and certain beliefs about bad luck and modes of transportation being the main concerns<sup>141</sup>.

## **Monitoring**

There were a number of important and feasible items selected by both the expert and practitioner panels (as seen in table 9). The steering committee believed that the concept of monitoring should be included within the bundle, as a reminder to clinicians of its importance. The monitoring of a patient is key to evaluating the need for and response to treatment. Other sepsis bundles include the use of monitoring techniques such as measuring hourly urine output or checking lactate levels<sup>13</sup>, in order to ensure users remember these important actions and act on them accordingly.

In a low-income setting, even the most basic of monitoring may be omitted and this can be due to a number of reasons, including lack of equipment or training. Therefore, including these within the bundle ensures users are aware of their importance and encouraged to carry them out. The individual elements to be monitored have been noted as per the Delphi results and it is suggested these elements should be monitored first.

Other sepsis bundles, such as “Sepsis Six” have developed toolkits and documentation according to the location of the patient e.g. in the community or in the emergency department and provide guidance accordingly<sup>51,70</sup>. Similar implementation tools will be necessary for the implementation of this low-income maternal sepsis bundle.

Many studies have looked at sepsis care in low-resource settings and have worked on developing specialised care bundles for this setting, although not necessarily for obstetric patients. For example, in 2012 Dünser et al collaborated with a global working group in

intensive care to develop recommendations for sepsis care in low-resource settings<sup>16</sup>. Structured literature reviews and discussions were held with leading practitioners in sepsis and intensive care. The outcome was two suggested care bundles to be used in sepsis management in resource-poor settings. This included the “acute care bundle” comprising of oxygen therapy, fluid resuscitation, early and adequate antimicrobial therapy and surgical source control<sup>16</sup>. The “post-acute care bundle” comprised of re-evaluation of antimicrobial therapy, deep vein thrombosis prophylaxis, glucose control and weaning of invasive support<sup>16</sup>.

The low-income maternal sepsis bundle could be categorised as an acute care bundle as it is advised to be used within 3 hours of admission, and therefore post-acute care is not covered within our bundle. It is interesting to see that the final components of this bundle comprise 3 of the 4 items suggested by Dünser. Oxygen therapy was deemed as fairly feasible and not very important by our Delphi stakeholders in both rounds (as seen in figures 15 and 19) and therefore did not make the final bundle. It is well known that sepsis is associated with the disordered delivery of oxygen to tissues<sup>12</sup>. Sepsis bundles such as the “Sepsis Six<sup>13</sup>” recommend the empirical administration of oxygen to keep oxygen saturations within normal levels (94-98%) and maintain good oxygenation. However, the equipment required to assess oxygen saturation and deliver oxygen are less available in low or lower-middle income countries and the costs of using such a sparse commodity are seen as lower down in the list of interventions that are the most feasible and important in the initial management of maternal sepsis.

Various implementation tools can be used to assist in the delivery of such a bundle. For example, a flow chart or checklist may assist in ensuring all steps have been carried out, listing them in an easy-to-read manner for the user. This can be especially useful in terms of monitoring, whereby practitioners may forget to measure and document important vital signs. Using such tools can allow practitioners to document the measurements they have taken and show when to act on certain results. Although advantages of using these tools are clear, in a low-income setting, the availability of the materials could be an issue. In addition, practitioners will require training on how to document and when to act on the results and escalate further.

### **Strengths & Limitations**

There are strengths and limitations to our study. Our Delphi study included a large number of participants from many different backgrounds, showing diversity within both of our stakeholder panels. The breadth of our responses shows that our results may be generalised to a large number of low and low-income countries. On the other hand, identification of the majority of the practitioner panel relied upon stakeholders cascading the link to fellow eligible colleagues, therefore the cohort sampled may not represent the full potential of the population.

In terms of sample size, according to the literature, many similar Delphi studies have had comparable numbers. Overall, 154 stakeholders were included in our Delphi study, which is alike to the recently published “global health competencies for postgraduate doctors” Delphi study carried out by Walpole et al in 2016<sup>142</sup>. This study sampled 250 doctors and other

health professionals in a similar modified Delphi approach with online and face-face consultations to determine global health curriculum items for postgraduate doctors in the UK. However, this is dependent upon the specific project as for example, a Delphi study carried out to establish consensus on the diagnostic criteria for Carpal Tunnel Syndrome, published in the USA in 2003, only included 14 stakeholders as they were looking to involve only specialists in the field<sup>143</sup>.

Another strength of our project is that we were able to reach consensus in just three iterations, ensuring we were able to reach a conclusion rapidly and with a clear consensus on the critical items for inclusion. The fact that we were able to complete the rounds online and not require face-face or telephone interviews also worked to our advantage, as it saved us time in obtaining results. In contrast, a limitation to the online responses, is that we missed out on the opportunity to discuss various questions face-face and transcribe the answers, which may have given us more detailed information that may have been useful at the analysis stage.

Although we had a high response rate for our expert panel, especially for round 3 where 9 of the 11 experts responded, this was not mirrored with our practitioner panel, which is another limitation that we encountered. The high response rate from the expert panel is perhaps due to the fact it was a smaller cohort and the experts were likely to be more engaged and motivated to participate in the process, as opposed to the practitioners who were selected at random.



The results from our study are important, as it shows this bundle development process has been robust, with broad stakeholder involvement from a large number of countries. The practitioners involved had recent practical experience and a deep knowledge of the realities of practicing in their setting. The use of an expert panel also allowed us to triangulate the views of the practitioner panel with those of the experts. It also ensured we were up to date with recent research and recognised new innovations that practitioners in LMIC may not be aware of.

### **Recommendations**

This study has highlighted the chance to change the way in which maternal sepsis is managed in low and lower-middle income countries. Now that this care bundle has been developed, we recommend that it should be operationalised in a low-resource setting. Various toolkits will need to be developed for its implementation.

A feasibility study to test the usability and practicality of the FAST-M bundle are currently underway and was commenced in April 2017 in Malawi. Following this, a large multi-centre cluster randomised controlled trial can then be carried out, to assess the efficacy of using this bundle in the management of maternal sepsis.

### **Conclusions**

The use of care bundles in sepsis is shown to improve clinical outcomes. Currently, for maternal sepsis in low and lower-middle income countries, the use of the available sepsis

bundles are inappropriate and not feasible. A clinically relevant and feasible maternal sepsis care bundle has been developed by a consensus forming process with a wide range of practitioners and experts. This low-income maternal sepsis bundle can be developed into a package to be implemented and tested in an appropriate setting in the near future.

## **CHAPTER 4: DEVELOPING AN EXPLORATORY THEORY OF CHANGE**

### **TO IMPLEMENT A MATERNAL SEPSIS CARE BUNDLE IN MALAWI**

## **ABSTRACT**

### **Background:**

A theory of change (TOC) is a method used to describe the way in which a programme can achieve a specific long-term outcome, through a logical sequence of intermediate outcomes<sup>144,145</sup>. It is in an iterative group process, undertaken through a series of workshops. Stakeholders undertake “backwards mapping” to identify the necessary pre-conditions required to achieve the long-term outcome. A theory of change approach can be used for the development and implementation of new complex packages or interventions.

### **Methods:**

A theory of change development process was undertaken involving multiple workshops, held as “in-country” meetings. These were held in various locations in Lilongwe, Malawi over a one-week period in May 2016. Stakeholders included doctors, researchers, clinical officers and nurse midwives, who offered enthusiastic and compelling ideas. The focus was on the newly developed FAST-M bundle for the management of maternal sepsis in low-income settings.

In total, 71 people participated in 6 theory of change workshops. Each of the proposed bundle elements were discussed in detail, outlining the key barriers and facilitators to its implementation, and ideas of how to overcome these. At the end of the weeklong programme of workshops, an action plan with the next steps was created, to assist in planning for implementation of the bundle.

**Conclusions:**

An exploratory theory of change has been developed to support plans for the implementation of a low-income maternal sepsis bundle. Plans for a feasibility study to pilot the implementation of the bundle in a low-income country setting are underway, and the outcomes of this will be used to develop the theory of change further.

**Keywords:**

maternal sepsis; bundle; theory of change; implementation; intervention development; stakeholder involvement

## INTRODUCTION

A theory of change (TOC) is a planning tool, used mainly in government and not-for-profit sectors, to develop solutions to complex social issues<sup>146</sup>. The development of a theory of change is a participatory process<sup>147</sup> which involves a group of stakeholders coming together to identify a “*long term outcome*” and then document how and why this goal will be reached<sup>146</sup>.

Undertaking a theory of change can help to show how a programme intends to meet the desired outcomes by addressing the problems that may arise<sup>148</sup>. It ensures boundaries are clarified and enables the team to outline the outcomes that are achievable as well as those that are beyond the scope of the programme in question<sup>148</sup>. Stakeholders can use this iterative process to understand and evaluate the underlying logic or rationale of a proposed program<sup>149</sup>.

Stakeholders undertake the process of “backwards mapping”, whereby the long term or ultimate outcome is identified first, followed by ascertaining the necessary immediate or intermediate outcomes, which are required to meet the long term goal<sup>148</sup>. This process usually culminates in the form of a TOC diagram, which is a graphical representation of the pathways, required to achieve the outcomes.

Developing a TOC involves proposing a number of interventions that can bring about the long-term goal. Each outcome proposed in the TOC require one or more “*indicators*” of success<sup>150</sup>. As implementation of the theory of change progresses, data is collected on the

indicators to monitor progress and ensure outcomes have been met. Indicators are usually measurable, observable and can be used to evaluate the progress and success of the TOC<sup>146,147</sup>

In addition to the outcomes and indicators, a TOC requires *“assumptions”*. These are conditions which the group recognise need to be in place in order for the outcomes to be met<sup>145,150</sup>. Throughout the TOC process, stakeholders must also explain the *“rationales”* for why the outcomes proposed are necessary preconditions to the long term outcome<sup>147</sup>.

The long-term outcome is a realistic goal, however there is an ultimate goal (also known as the *“impact”*) that can be placed above the long-term goal highlighting the impact of that particular theory of change<sup>146</sup>. A dashed line can be added to the TOC diagram, called the *“accountability ceiling”* which distinguishes it from the long term outcome<sup>146</sup>. The ultimate goal transcends what the group feel they can achieve through their own efforts, therefore everything the group feel they can achieve is placed below the accountability ceiling<sup>147</sup>.

Development of the theory of change usually takes place over a number of meetings or workshops, held by a facilitator or group of facilitators. Stakeholders are consulted on their opinions throughout the process until a final causal pathway is developed. Taplin et al advise that the average number of stakeholders at each meeting should not be less than 6-8 and each meeting should last at least 2 hours in length<sup>150</sup>. There is no limit suggested on the number of meetings but to be continued until the outcomes are validated and agreed upon by the stakeholders<sup>148</sup>.

Materials required for these workshops include flip charts, post-it notes and coloured pens or markers. Stakeholders often write their ideas on separate sheets of papers or notes and facilitators then work through them, either in small groups or as a larger group, exploring the themes and ideas presented<sup>150</sup>. During workshops, team members elicit the barriers and facilitators to the implementation of the theory of change and develop tailored outcomes. Hailemariam et al identified that one of the most important goals of a TOC workshop is to “elicit stakeholder buy-in”<sup>151</sup>. This is important to ensure stakeholders feel involved from the beginning by ensuring they are involved in the development of the final intervention<sup>151</sup>.

We have recently carried out a global consensus to develop a new care bundle for the initial management of maternal sepsis in low-income countries. The bundle consists of five well-known interventions, that when carried out together, we hope will improve maternal sepsis care. The items included within the bundle include: administration of intravenous fluids; early administration of intravenous antibiotics; identification and removal of the source of the infection; transport to the appropriate location of care and monitoring of the mother and neonate. Components of the bundle can be remembered by the acronym, *FAST-M*.

In this chapter, we demonstrate the use of the theory of change approach explore the barriers and facilitators to the implementation of this bundle, through a series of in-country workshops held in Lilongwe, Malawi. This framework will help to identify the interventions and desired outcomes for a pilot study, and will be followed through by members of the University of Birmingham team and our colleagues based in Lilongwe, Malawi. This exploratory theory of change can then be evaluated and refined using the pilot study results.



## **METHODS**

### **Setting & Background Work**

Development of this TOC took place through workshops and meetings held in Lilongwe, the capital city of Malawi. The University of Birmingham Medical School and College of Medicine in Malawi work together frequently on global maternal health projects, with academic clinicians regularly carrying out research projects at facilities in both Blantyre and Lilongwe.

Once the Delphi study was completed and the maternal sepsis bundle for low-income countries was developed, we decided to organise meetings with stakeholders in Lilongwe to understand the needs and requirements of healthcare workers in the area and discuss how to successfully implement this bundle, using a theory of change approach.

Lilongwe was chosen as the destination as it is the capital city of Malawi and therefore more accessible for clinicians and researchers to reach for the meetings. Three months before the meeting, we sent invitations out to notable researchers, doctors, clinical officers, nurse-midwives and technicians in Malawi inviting them to take part in a weeklong programme to discuss the new bundle. A “welcome pack” with information on the project so far and relevant important papers and reports was also forwarded to stakeholders two weeks prior to the meeting, so that they were well informed about the project thus far. Many stakeholders had already taken part in the Delphi study and were aware of the plans to develop and implement this low-income maternal sepsis bundle.

In addition to our own work on developing the sepsis bundle, other members of our research team had recently undertaken a data collection project in Blantyre, Malawi to establish resource availability for the management of maternal sepsis in the region. Information from this cross-sectional study was also useful to highlight the difficulties healthcare workers in Malawi face when managing patients with maternal sepsis and the resources already available to them.

In total, six theory of change workshops took place. Three were formal workshops with a variety of delegates with a background or interest in maternal sepsis. The remaining three workshops were site visits, to health centres and hospitals in the region, to discuss pertinent questions with healthcare workers working there.

### **Site Visits**

The first site visit took place at Dzaleka Health Centre and Refugee Camp. Five clinical researchers from the University of Birmingham met with a clinician, two nurse-midwives and administrator. We asked questions in order to better understand the resources available to the staff in this health centre and the region that they cover. We discussed the barriers to providing safe and efficient care for women presenting with signs of sepsis and how we may overcome them. The new sepsis bundle was introduced and we were able to discuss how this might be introduced and some useful tools that would help with its implementation.

The same day, we arranged a larger stakeholder site visit at Dowa District Hospital. Here, we met with the District Nursing Officer (DNO) in addition to 13 clinical officers, nurse-midwives

and technicians/assistants. The workshop began with members introducing themselves and describing their background. Although all stakeholders could speak English, one of the nurse-midwives volunteered to translate from English to Chichewa (Malawi's national language), in order to ensure all stakeholders could follow the meeting.

We began by introducing the bundle, outlining its purpose and plans for its implementation. Each of the five components of FAST-M were discussed in detail. We covered the issues healthcare workers in the hospital face regarding sepsis management and what was available in terms of resources and current practice. The main concerns were identified and ideas for solutions to these were offered. The session, which lasted just over an hour concluded with ideas for implementation of the bundle, including helpful resources such as monitoring tools and training sessions.

The final site visit took place at Mitundu Hospital, located further out in the Lilongwe district. This community hospital is a referral centre for 15 health centres with 60, 000 patients within its catchment area. We met with the clinical officer and nurse-midwife in charge to get an introduction to the facilities and challenges they face on a daily basis. As with the other site visits, we introduced the newly formed FAST-M bundle and identified how we can implement this in sites such as Mitundu Hospital, within Malawi. It was important to again discuss the implementation tools, which would be useful including posters, pocket cards and leaflets. The main barriers to sepsis management were discussed fully and solutions to these issues were suggested.

### **TOC Workshops**

The first formal TOC workshop was held on the third day of the trip. This was the first of three days of workshops to discuss the implementation of the FAST-M bundle. All three workshops were held at Kamuzu College of Nursing in Lilongwe. In preparation, in addition to the delegate packs created, materials such as notebooks, pens and markers were available for note taking. Large sheets of white paper that could be stuck to walls were used as temporary whiteboards, which proved useful during group work.

As for other TOC meetings, individual members introduced themselves and their backgrounds. Doctors, nurse-midwives and clinical officers were in attendance, along with research and administration staff.

In addition to the five clinical researchers from the University of Birmingham, there were representatives from a number of organisations. This included two clinical officers who represented the Malawi Association of Obstetric Clinical Officers (MAOCO) as well as delegates from a variety of charities and NGO's such as: Save the Children, PACHI (Parent and Child Health Initiative) and JHPIEGO (Johns Hopkins Program for International Education in Gynecology and Obstetrics). There were also representatives from the Malawi College of Medicine and Kamuzu College of Nursing as well as the Reproductive Health Unit (RHU) of the Republic of Malawi's Ministry of Health. We were grateful to be also joined by the Chief Executive of the UK Sepsis Trust and Chief Executive Officer of the Global Sepsis Alliance (GSA), who is a critical care doctor in the UK. His successful work in developing the "Sepsis Six" bundle in the UK gave an interesting and relevant perspective. In total, there were 18

delegates on the first day of the workshops, followed by 14 on the second day and 12 on the final day.

We began by introducing our project and proposing our long-term goal: to improve the initial management of patients with maternal sepsis in low and lower-middle income countries. An interactive PowerPoint presentation was given on the background of the project and the work done thus far, including information on our meetings with the World Health Organization (WHO) and possible collaboration. This first meeting consisted of a full-day programme with group discussions in the morning and smaller breakout group sessions in the afternoon, followed by a plenary session.

The morning session covered the main issues and challenges in delivering high quality sepsis care to pregnant and postpartum women. As a group, we discussed our long-term goal and discussed how feasible and realistic this is. Delegates were seated around a large square table so that discussions could be had comfortably within the group. Information was given on the current practice and guidelines and the role of the government and Ministry of Health, which helped us to understand how implementation of this bundle may be streamlined.

We then split into three main groups. Each group discussed two bundle elements as well as how to recognise maternal sepsis, by use of a trigger (a project currently underway by the WHO maternal sepsis team). The three groups covered the following: Fluids & Transport, Monitoring & Trigger and Antibiotics & Source Control. Delegates were assigned an hour to

discuss what was needed to make the bundle successful in these areas, thinking about the people, equipment and communication requirements in addition to systems management and teamwork. Delegates were also asked to consider the social, political and legal issues and to identify barriers to implementation of the bundle and solutions to these.

The small groups then presented to the rest of the group and opinions were invited from other members, throughout the session. Delegates were enthusiastic and presented very well rounded and thought out ideas. Resources used during this process included the temporary whiteboards, markers and notepads/pens.

The plenary session for this day used post-it notes to allow delegates to come up with individual ideas, which could then be grouped together. During this part of the workshop, delegates were asked how FAST-M could be made so easy that everyone would use it, as well as finding out what information healthcare professionals would want to know about its use. This session culminated in a visual representation of the ideas presented in the form of a post-it note histogram. The short-term outcomes required to achieve our long-term goal were also suggested.

During the second workshop day, we focussed on the implementation plans including the possibility of a pilot study to assess the feasibility of the FAST-M bundle, and its implementation within the Malawian Healthcare System. Information was gained on the design and outcomes for the study in addition to suggestions of possible pilot sites within Lilongwe and the surrounding areas.

The final workshop centred on tools that could be used for the bundle implementation process, for triage in a hospital and health centre setting. Examples of tools, pathways and bundles already in use in the Malawian healthcare system were reviewed and this was useful in identifying what could work in the region. Preliminary designs for a FAST-M proforma were undertaken and plans for the pilot study were discussed again in detail. An action plan with the important post-workshop plans was created and will be followed up by members of both the University of Birmingham team and colleagues based in Malawi.

### **Data Collection**

Data was collected through scribing in detail each of the discussions, in addition to recording the information from the post-it notes & whiteboard collection. No personal information was obtained from participants and no formal ethical clearance was required. Stakeholders gave informed consent to participate prior to the meeting, upon accepting the invitation to attend.

### **Post-Meetings Work**

Following the workshops, minutes from the meetings were used to create an executive summary report, which was sent to all delegates in addition to ministry officials and other relevant personnel (see appendix 5). Work began on developing the exploratory theory of change diagram and the information obtained from the workshops was used to identify the important outcomes as well as the facilitators and barriers to its implementation.

## RESULTS

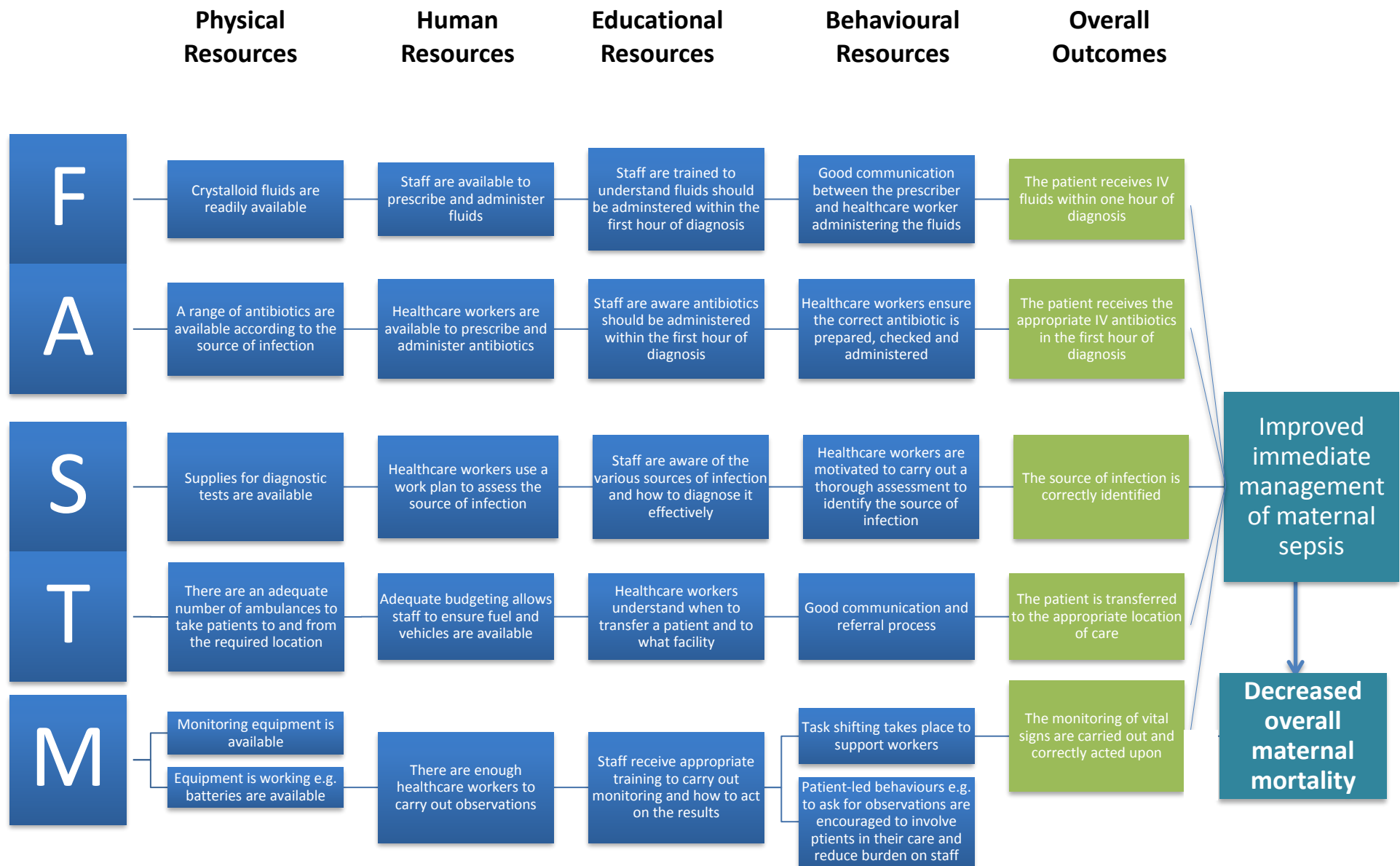
A final theory of change (TOC) diagram has been developed through six theory of change workshops held in Lilongwe, Malawi. This TOC diagram shows the pathway and interventions required to achieving the overall long-term goal and highlights the important barriers and facilitators to implementing the FAST-M bundle.

### Outcome Pathway

Figure 21 shows the preliminary exploratory theory of change diagram. The long-term outcome is highlighted as *“Improved initial management of maternal sepsis”* followed by the impact, which is to *“decrease maternal mortality”*. In order to achieve this long-term goal, there are outcomes to be achieved in various sectors relating to the use of the FAST-M bundle. The diagram highlights the individual objectives for each part of the bundle (Fluids, Antibiotics, Source Control, Treatment and Monitoring) under the sub-headings of Physical Resources, Human Resources, Educational Resources and Behavioural Resources. Identifying the individual needs and objectives in this way allows us to establish the short-term goals required to meet the long-term outcome.

Below the flowchart, is an arrow outlining the key assumptions over the course of the model. These are conditions or resources that already exist or are expected to be in place in order to carry out the theory of change successfully<sup>147,152</sup>. These are different to the outcomes, which represent interventions or conditions that do not already exist and need to be brought about with the aid of the TOC<sup>150</sup>.







### Key Assumptions

- Assurance of buy-in and backing from the Malawi Ministry of Health Reproductive Health Unit (RHU) and ability to integrate with co-existing projects such as the Safe Motherhood Initiative
- Adequate funding to be secured to pilot the use of the bundle, appropriate for a multi-centre feasibility study in and around Lilongwe, Malawi
- Engagement of staff at all levels and a willingness to learn new skills and techniques
- Co-operation of staff to adhere to the bundle guidelines or protocols
- Staff are given the time and resources to attend training sessions to use the bundle
- Adequate resources to be available to staff to successfully complete bundle paperwork including printing facilities to create work plans, booklets and posters

**Figure 21:** Theory of Change Outcomes Pathway Diagram

## Interventions & Rationales

Interventions are the action points to be undertaken as part of the theory of change in order to reach the long-term goal and rationales are the logic and reasoning behind these interventions<sup>147</sup>. Some of the main interventions and rationales, which are highlighted on the TOC diagram are described in table 10 below, and are grouped as per the sub-categories of the diagram.

**Table 10:** Interventions and rationales for TOC diagram

Preliminary Outcome	Interventions	Rationales
<b>FLUIDS</b>		
Crystalloid fluids are readily available	Improve communication between facilities and hospitals, ensure champions/representatives involved	Regular checks and ensuring individuals are responsible for certain items will help to prevent stock issues of basic fluids such as crystalloids, which are recommended in sepsis
Good communication between prescriber and person administering fluids	<ol style="list-style-type: none"> <li>1. Prescriber should follow guidance outlining fluid choice and rate of administration. Instructions should be relayed to person administering fluids.</li> <li>2. Healthcare workers use FAST-M resource booklet and mobile application for additional support</li> </ol>	Clear information on how to prescribe fluids will ensure fluids they are prescribed effectively. Good communication will ensure fluids are given in a timely manner – within the first hour of diagnosis

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**ANTIBIOTICS**

Healthcare workers are available to prescribed and administer antibiotics	<ol style="list-style-type: none"><li>1. Healthcare workers receive training and practice skills in onsite training simulations and drills</li><li>2. Healthcare workers use FAST-M resource booklet and mobile application for additional support</li></ol>	Training will improve healthcare workers confidence in managing cases and knowing which antibiotics to prescribe for different patients
A range of antibiotics are available, according to the source of infection	Improve communication between facilities and hospitals, ensure champions/representatives involved	Regular checks and ensuring individuals are responsible for certain items will help to prevent stock issues and ensure different antibiotics are available

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**SOURCE CONTROL**

Supplies for diagnostic tests are available	Improve communication between facilities and hospitals, ensure champions/representatives involved	Ensuring regular checks and having specific job roles will ensure supplies can be ordered in time and improve stock issues
Healthcare workers are motivated to carry out thorough assessment of patient to identify the source of infection	<ol style="list-style-type: none"><li>1. Work plan will contain visual checkpoints for sources of infection (on a human figure), which can help healthcare workers to remember to carry out thorough history, examination and diagnostic tests. Checklists can also be used</li><li>2. Healthcare workers use FAST-M resource booklet and mobile application for additional support</li></ol>	Posters and flowcharts have been shown to help clinicians and nurses remember important points in terms of diagnosis and management plans

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**TRANSPORT**

There are an adequate number of ambulances to take patients to and from the required location	Maintain involvement of broader stakeholders (e.g. ministry) and NGO's to ensure ambulance numbers present	To ensure ministry and other officials aware of problems relating to ambulance issues
Good communication and referral process	Healthcare workers use a template referral form or tool to ensure every referral follows the same format. They can receive feedback for doing this correctly which will encourage them to do it more often	This will ensure important information such as observations, treatment given and treatment to be received is given and ensure safe transfer of care
Adequate budgeting allows staff to ensure fuel and vehicles are available	Maintain involvement of broader stakeholders (e.g. ministry) and ensure local champions involved to oversee fuel issues	Individuals taking responsibility will ensure issues with fuel supply are identified and dealt with early

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**MONITORING**

Equipment is working e.g. batteries are available	Audits to check stock, or assign an individual to ensure stock checked. Local champions to ensure concerns with equipment are highlighted early	Highlighting concerns with equipment early can help to ensure working equipment is available and monitoring of patients can be more streamlined
Monitoring equipment is available	Assign individual is responsible for keeping track of equipment location or giving it a permanent location e.g. attached to a wall	Keeping equipment in one location or ensuring it is returned to its location will help to prevent equipment going missing
There are enough healthcare workers to carry out observations	Task-shifting should be considered here, so that observations can be carried out by support workers such as patient attendants instead of nurse-midwives	Task shifting can help to shift the burden of observations to non-trained staff so that nurse-midwives and other technicians can complete other jobs. Patient attendants can use tools to ensure they

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		escalate to nurse-midwives and clinicians at the appropriate time
Staff receive appropriate training to carry out monitoring and how to act on the results	<ol style="list-style-type: none"> <li>1. Healthcare workers follow guidance from a care pathway and screening tool e.g. trigger tool or MEOWS chart</li> <li>2. Healthcare workers use the FAST-M resource booklet and/or mobile application to follow guidance on how to act on certain observations and escalate care</li> </ol>	<p>The screening tool will allow healthcare workers to recognise which patients require observations. The tool will alert healthcare workers to how often observations need to be completed and when to escalate further</p> <p>Using the applications will ensure healthcare workers are reminded of how to act on observations and escalate appropriately</p>

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## DISCUSSION

The development of a theory of change can help to plan the implementation of a complex intervention in challenging situations. There have been recent examples of the TOC approach being used in healthcare, and specifically in a low-income country setting. Hailemariam et al explored the use of a theory of change approach to develop a mental health care plan in a low-resource setting<sup>151</sup>. They describe the use of a TOC to support the implementation of a new care plan that is designed to help tackle this challenging issue of care for mental health patients in rural areas of low-income countries such as Ethiopia<sup>151</sup>. They successfully engaged with local stakeholders and used the TOC approach, which they felt was a strong component in the development of the new mental health care plan. They found that the process helped to elicit stakeholder buy-in to the project and reduce uncertainties about its implementation. Hailemariam et al suggest a TOC approach can be used to plan for many different complex health interventions in low-resource settings<sup>151</sup>.

### **Main Findings**

The theory of change is considered both a process and a product<sup>153</sup> and has been used in this instance to evaluate the implementation of the FAST-M low-income maternal sepsis bundle. Our project took place in Lilongwe, Malawi over a one-week period with input from a variety of respected stakeholders. An exploratory theory of change diagram has been produced and a number of short-term outcomes that should be met were highlighted, in order to use the FAST-M maternal sepsis bundle and reach the long-term goal of *“Improved initial management of maternal sepsis in low and lower-middle income countries”*. Key

assumptions were identified for the successful use of the TOC and it is recognised that organisational change, with the help of an implementation committee, should take place in order to assist in the implementation of the bundle.

### **Strengths & Limitations**

There are many strengths to using an exploratory theory of change approach in the development and implementation of a new healthcare intervention, specifically for use in another country. The experience of holding the workshops in the country where the bundle is intended to be used, allowed us to understand how maternal sepsis care is practiced currently in Malawi and the challenges that they face on a day-to-day basis. We were able to understand what interventions have been successfully used in Malawi and hear from healthcare workers “on the ground” who deal with cases of maternal sepsis daily. The fact that we were able to hear from such a diverse group of stakeholders was another advantage of our theory of change process. This included ministry and government officials as well as NGO representatives who were able to give us insight into the difficulties of the Malawian healthcare system and the resources that are available. In addition, nurses and clinicians working in the health centres and hospitals, who diagnose and treat patients everyday, were able to give us a valuable insight.

Using this TOC approach, we were able to plan an intervention with strong involvement from an engaged community base. Involvement of the community has been shown to ensure sustainability of the outcomes presented<sup>151</sup>. It is also an effective method to engage with and obtain buy-in from multiple stakeholders<sup>145</sup>. This approach has also enabled us to



highlight the barriers to implementation of the bundle and develop strategies, with those involved, on how to overcome these.

It is recommended that a TOC can be used to pilot the feasibility of an intervention<sup>154</sup>. Using a TOC in this way can help to identify any gaps in the knowledge and alert the team to any research questions that need to be further addressed during the pilot study stage. Therefore, the TOC can be used as a guide when planning the feasibility study for the bundle and can be further adapted and improved throughout the process, using feedback from the study as a guide.

However, there are some limitations to using a TOC approach. Although the TOC can be used to guide feasibility, it is not practical to assess the challenges that may be faced throughout the implementation process and due to the nature of TOC development, all assumptions and interventions are suggested at the beginning of the process. It is natural therefore for the TOC to be altered and adapted as described above.

Also, due to the backwards-mapping nature of the development process, often there may be too many outcomes or complex interventions suggested which could be difficult to achieve. It is important to ensure the outcomes are simple, smart, realistic and achievable by those involved.

Although we had a wide variety of stakeholders included within our TOC development process and had experiences from doctors from both the UK and Malawi in Obstetrics and

Critical Care, we were missing input from other specialties including microbiology and infectious diseases. Unfortunately, the doctors contacted in both UK and Malawi were unavailable to attend, however offered their services and were happy to be contacted with queries throughout the TOC process. Involvement of practitioners from these specialties may have highlighted some other issues including the local guidance for antibiotics and microbiology resistance patterns, which may have proved useful in the TOC planning process.

### **Conclusions**

Through a series of TOC workshops held in Lilongwe, Malawi, we have created an exploratory theory of change diagram to support the implementation of the low-income maternal sepsis bundle, FAST-M. We recommend the use of this TOC to guide and design an appropriate feasibility study that may be used to pilot the new bundle in a low-income country setting, such as Malawi, in the near future. The evidence base gained from the results from the feasibility study will be then used to refine and formally develop the theory of change, with involvement of the key stakeholders in the final development process.

## **CHAPTER 5: DISCUSSION**

## **SUMMARY**

The objective of this thesis, as set out in chapter 1, was to develop a new care bundle, which can be used in the initial management of maternal sepsis, in low and lower-middle income countries. This has been accomplished through an international Delphi method, which achieved consensus on the most important and feasible items to be included in the low-income maternal sepsis bundle, leading to the development of the FAST-M maternal sepsis bundle.

In addition, we have undertaken a systematic review and meta-analysis on the use of general care bundles in low and lower-middle income countries, establishing a background on the efficacy of bundle use in these countries. Finally, following production of the bundle, an exploratory theory of change framework has been created following in-country meetings held in Malawi, to help facilitate the implementation of the bundle.

In this chapter, the main findings of the thesis will be summarised, followed by the recommendations for clinical practice and implications for future research.

### **Care Bundles in Low Resource Settings**

The question we aimed to answer with this systematic review and meta-analysis was whether the use of care bundles, in a variety of settings, in low and lower-middle income countries (LMIC), improved the care patients received overall. Additional outcomes included a reduction in the incidence of infection and reduced mortality. The studies selected

included only adult patients in LMIC and compared the use of bundled care to usual care. Both randomised and non-randomised controlled studies were selected and the care bundles varied from general sepsis bundles to specific bundles for ventilator-associated pneumonia (VAP) and others. Of the ten studies included, five were included in a meta-analysis for incidence of infection. There was an overall significant reduction in the incidence of infection with bundled care (rate ratio 0.58, 95% confidence interval 0.48 to 0.70,  $p<0.001$ ).

Further results were displayed as forest plots without summary measures and could not be meta-analysed due to variations in study design. However, from the figures (3 and 4 respectively), it is suggested that bundled care was not associated with a decrease in the risk of mortality or a reduction in severity score (APACHE II).

These results show that care bundles can significantly reduce the incidence of infection in LMIC, compared to usual care. However, only ten studies were included in this review and further research with a larger number of studies, from similar study designs would need to be included in a meta-analysis in order to ascertain if the use of care bundles can significantly reduce mortality. Given the findings of this systematic review and meta-analysis, the development of a care bundle created specifically for use in LMIC could help to improve the care these patients receive and improve the management of conditions such as sepsis. It highlights the need for further research into improving sepsis care in these countries and the development of further tools including an LMIC specific bundle, to help health professionals recognise the importance of managing sepsis early.

### **International Delphi Consensus**

In this chapter, our main aim was to develop a consensus based care bundle for use in the initial management of maternal sepsis in low and lower-middle income countries (LMIC). This was done using a three stage iterative Delphi method. Following a detailed literature review, a comprehensive long-list of items was created for inclusion within the bundle. Advice was sought from an advisory panel of experts prior to the final selection of bundle items.

For the first round of the Delphi, an online questionnaire was made and sent to healthcare professionals working in LMIC. Participants were asked to rank each treatment and monitoring item on both importance as well as feasibility (in a health centre and hospital setting). For the second round, the same questionnaire was sent to a panel of selected international experts in the field. The final round of the Delphi involved feeding back the results from the first two rounds to all participants, to identify if consensus had been reached. Over 150 participants from 34 countries in total took part. Consensus was achieved at the end of round 2 and confirmed in round 3. The final items selected were:

- Administration of IV fluids
- Administration of IV Antibiotics
- Identification and removal of the source of the infection
- Transport to the appropriate higher-level care facility
- Monitoring for both mother and baby

These final elements were subsequently summarised with the acronym **FAST-M** to assist practitioner recall. Following the development of this robust, evidence-based low-income maternal sepsis bundle, the next phase would be to pilot this bundle in a feasibility study in a low or lower-middle income country. Based on the results of this pilot study, a multi-centre randomised controlled trial can then be undertaken to assess the efficacy of using this bundle in the management of maternal sepsis. If successful, this could change the face of maternal sepsis management in low-income countries, and help to provide a unique and easy-to-follow framework for healthcare professionals, allowing them to recognise and initiate sepsis management earlier.

Looking at the literature, there are very few sepsis care bundles that have been created specifically for use in LMIC. One example is the bundle created by Dünser et al in 2012, who developed an “acute” and “post-acute” bundle for use in both children and adults presenting with sepsis in resource-limited settings<sup>16</sup>. The authors carried out a thorough literature review and found that the evidence for the management of sepsis in low-resource settings was lacking<sup>16</sup>. As a group, they therefore identified which of the interventions would be the most useful in a low-income sepsis bundle. Members of the Global Intensive Care working group of the European Society of Intensive Care Medicine and the World Federation of Paediatric Intensive and Critical Care Societies voted on the interventions presented, at an international meeting in 2012. Their findings resulted in two bundles to be created, one in the immediate management of sepsis “acute care bundle” and one for the ongoing management of sepsis “post-acute care bundle”. The acute care bundle consists of oxygen therapy, fluid resuscitation, early and adequate antimicrobial therapy and surgical source

control. The post-acute care bundle includes: re-evaluation of antimicrobial therapy, deep venous thrombosis prophylaxis, glucose control and weaning of invasive support. The authors suggested implementation of these guidelines in a number of ways including audit/feedback.

The FAST-M bundle is similar to Dünser's acute care bundle in a number of ways. Antibiotics, fluids and source control are noted in both bundles. However the FAST-M bundle does not recommend routine oxygen therapy and Dünser's bundle does not discuss transport to the appropriate location and distinct monitoring. From our Delphi study, oxygen was deemed as less important than other treatment items by both panels. Only 32.9% of practitioners gave oxygen therapy a maximum score for importance of 5/5 (see figure 9) and only 9.1% of our expert panel gave it a score of 5/5 (see figure 17). On the scatter plot diagram for both practitioners and experts, it is ranked fairly low when plotted among other treatment items in terms of feasibility (as shown in figures 15 & 19). This shows that our stakeholders do not necessarily think oxygen is a core item required for the low-income maternal sepsis bundle. This could be for a number of reasons including lack of resources or monitoring of oxygen saturations.

This preliminary FAST-M bundle has been created with the intention of assisting healthcare workers in the initial management of maternal sepsis in low and lower-middle income countries. Following an initial pilot study, any amendments or improvements can be made to the bundle, as necessary in order to take it further and allow its implementation into national guidelines.



### **Exploratory Theory of Change**

A theory of change is often used to help facilitate the implementation of complex healthcare interventions. Chapter 4 describes the process of the development of a theory of change, for use in the implementation of the FAST-M low-income maternal sepsis bundle.

Through a series of in-country meetings which took place in Lilongwe, Malawi in May 2016, we heard from a number of local, national and international stakeholders and discussed the bundle, in addition to how best to implement it in a low-income country setting. Through group discussions, an exploratory theory of change diagram has been produced outlining the short-term outcomes to be achieved, categorised by the different parts of the bundle. During the implementation process, meeting these short-term outcomes will help to achieve the long-term goal of *“Improved initial management of maternal sepsis in low and lower-middle income countries”*.

From the in-country meetings, we were better able to understand the needs of healthcare workers in low-income countries such as Malawi. The important information gained will allow us to plan the implementation of the bundle for the feasibility study including the resources and tools required to ease the implementation process. Following the proposed feasibility study, the theory of change can be formally developed and improved, in order to be used for the next stage of operationalisation and implementation.

## RECOMMENDATIONS & IMPLICATIONS FOR FUTURE RESEARCH

The new low-income maternal sepsis bundle is a valuable development in maternal sepsis research and if successful, could help to improve sepsis care that women receive in LMIC. As mentioned previously, the ultimate aim is to trial the FAST-M bundle in a multi-country cluster randomised controlled trial. However, prior to this, a feasibility study should be undertaken in low-income country to pilot the bundle. Currently, the University of Birmingham team are working with the corresponding team in Malawi to undertake a feasibility study in a number of healthcare centres and hospitals in the Lilongwe region. Results from this study will prove to be especially useful in assessing the efficacy of the use of the FAST-M bundle in the initial management of women with maternal sepsis in Malawi and form the basis of future trials.

This project has also enabled our team to work with the World Health Organization, who have supported the work we have undertaken to develop the FAST-M bundle. As a result, members of our team have attended global sepsis workforce meetings to discuss the future of maternal sepsis care in low-resource settings and this has enabled the team to collaborate with them on their recently developed new definitions of maternal sepsis. The on-going collaborative work with the WHO & Jhpiego's *"Global Maternal and Neonatal Sepsis Initiative"* will allow us to continue the advances in the maternal sepsis research field and hopefully improve the management of maternal sepsis, focussing on this important cause of maternal and neonatal mortality worldwide.

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## **APPENDICES**

## APPENDIX 1: SYSTEMATIC REVIEW SEARCH STRATEGY

((("south america"[MeSH Terms] OR "central america"[MeSH Terms]) OR "latin america"[MeSH Terms]) OR "indian ocean islands"[MeSH Terms]) OR "indonesia"[MeSH Terms]) OR "pacific islands"[MeSH Terms]) OR "philippines"[MeSH Terms]) OR "middle east"[MeSH Terms]) OR "africa"[MeSH Terms]) OR "asia"[MeSH Terms]) OR "developing countries"[MeSH Terms]) OR "europe, eastern"[MeSH Terms]) OR ("georgia"[MeSH Terms] OR "georgia (republic)"[MeSH Terms])) OR (low income countries[Title/Abstract] OR low income country[Title/Abstract])) OR (middle income countries[Title/Abstract] OR middle income country[Title/Abstract])) OR (developing countermeasures[Title/Abstract] OR developing counterparts[Title/Abstract] OR developing counties[Title/Abstract] OR developing countr[Title/Abstract] OR developing countries[Title/Abstract] OR developing countries,[Title/Abstract] OR developing country[Title/Abstract])) OR resource-poor[Title/Abstract]) OR resource-limited[Title/Abstract]) OR africa[Title/Abstract]) OR south america[Title/Abstract]) OR middle east[Title/Abstract]) AND ((((((bundle[Title/Abstract] OR bundle'[Title/Abstract] OR bundle's[Title/Abstract] OR bundlebranch[Title/Abstract] OR bundled[Title/Abstract] OR bundled'[Title/Abstract] OR bundledp[Title/Abstract] OR bundleflower[Title/Abstract] OR bundleia[Title/Abstract] OR bundleless[Title/Abstract] OR bundlelike[Title/Abstract] OR bundler[Title/Abstract] OR bundlers[Title/Abstract] OR bundles[Title/Abstract] OR bundles'[Title/Abstract] OR bundles5[Title/Abstract] OR bundlesheath[Title/Abstract] OR bundlesheaths[Title/Abstract] OR bundlesmembranes[Title/Abstract] OR bundless[Title/Abstract] OR bundlesto[Title/Abstract] OR bundlet[Title/Abstract] OR bundlets[Title/Abstract] OR bundlewere[Title/Abstract]) OR care bundle[Title/Abstract]) OR "care package"[Title/Abstract]) OR "quality improvement"[Title/Abstract]) OR (multi dimensional approach[Title/Abstract] OR multi dimensional approaches[Title/Abstract])) OR (early goal directed therapies[Title/Abstract] OR early goal directed therapy[Title/Abstract]))

## **APPENDIX 2: ADDITIONAL INFORMATION SHEET FOR DELPHI PARTICIPANTS**

### **Development of a Care Bundle for the Management of Maternal Sepsis in Low-Income Countries**

Many thanks for considering taking part in this survey which will contribute to our project in developing a care bundle for the management of maternal sepsis in both low and lower-middle income countries (as defined by the World Bank<sup>1</sup>).

Sepsis during pregnancy and childbirth is a major cause of maternal mortality globally<sup>2</sup>. Over 5 million cases of maternal sepsis occur every year<sup>2</sup>, with significantly more cases identified in low income countries<sup>3</sup>. Sepsis is usually defined as systemic evidence of infection in the presence of an infection<sup>4</sup>. The signs of maternal sepsis can be different to that of a non-pregnant patient and often patients can deteriorate rapidly<sup>5</sup>, therefore it is important for clinicians to be aware of the signs of sepsis as well as have a robust method of initially managing maternal sepsis in order to reduce mortality rates.

In order to manage sepsis effectively, a number of care bundles have been produced including those of the Surviving Sepsis Campaign<sup>6</sup> and the “Sepsis Six” care bundle<sup>7</sup>. The implementation of these bundles has been shown to reduce mortality<sup>8</sup> by up to 44% and improve the overall care given.

However, in low income countries, clinicians have been unable to implement the elements of these kinds of sepsis bundle in the initial management of their patients presenting with sepsis<sup>9</sup>. Specialists in these countries see it as unsuitable, given the limited resources available<sup>10</sup>. A maternity specific bundle has also not been widely used in these settings. It is important to ensure mothers living in low income countries will have access to timely, evidence based, and reliable care; when presenting with signs of sepsis. This can be achieved by creating a care bundle specific to the needs of maternal sepsis in low and low-middle income countries. A specialised care bundle for the management of maternal sepsis will provide an evidence-based framework that can be used to commence treatment promptly and safely. This project will address this important global need. Having developed this bundle we then plan to robustly test it to see if it does offer a benefit above usual care.

In order to create this bundle, we will be using a modified Delphi method, a consensus forming tool that aims to collect and aggregate expert opinion in order to agree on a certain action or decision<sup>11</sup>. This will involve members of the Delphi group completing questionnaires or being interviewed in a number of rounds, in order to agree on a conclusion. Participants then review a report of results and can further amend or justify their responses until a consensus is formed.

We will carry out at least two rounds of the Delphi. The first will be in the form of this short on-line survey to determine the importance of different elements in the bundle and how feasible their implementation will be. The results from these questionnaires will then be

collated and members of an expert panel will be interviewed to provide further insights. The second round will include ranking of the interventions according to importance and relevance, and adding any relevant comments at this time. If at this point, a consensus has been reached regarding the most important elements of the bundle, the Delphi will be complete. However, if required, a third round will commence whereby we will ask Delphi members to review the list again and provide final input.

We thank you again for taking part; your responses will be invaluable to our research. If you have any further questions or would like to find out more, please don't hesitate to contact one of our researchers via email at: [REDACTED].

Kind Regards,

University of Birmingham Global Maternal Health Sepsis Team, Birmingham, UK

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  7. Daniels R et al. The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. *Emerg Med J* 2011;28:6 507-512
  8. Damiani et al. Effect of performance Improvement Programs on Compliance with Sepsis Bundles and Mortality: A Systematic Review and Meta-Analysis of Observational Studies. *PLOS ONE*. 2015 May. 10(5) 1-24
  9. Dünser, M et al. Recommendations for sepsis-management in resource-limited settings. *Intensive Care Med*. 2012. 38:557-574.
  10. Bataar, O et al. Nationwide survey on resource availability for implementing current sepsis guidelines in Mongolia. *Bulletin of the World Health Organisation*. 88:839-846. (2012)
  11. Durand M, Chantler T. Principles of Social Research. Second Edition. 2014 (Open University Press). P64-65.

### APPENDIX 3: COPY OF QUESTIONNAIRE USED IN ROUND ONE & TWO OF THE DELPHI STUDY

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1. Which country do you mainly work in?

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2. What is your job title?

Title

Other:

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3. What setting do you work in?

Setting

Other:

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4. In the last six months, have you managed a patient with maternal sepsis?

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5. In your opinion, how **important** are the following items in the initial **treatment** of severe maternal sepsis (e.g. to be initiated within 3 hours) in low and low-middle income countries?

Please only think about the importance of each item. Feasibility will be asked about later in the survey.

Please rate the following:

	1 = very un- important	2	3	4	5 = very important
Administer Intravenous Fluid	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Obtain venous access	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Administer antibiotics early	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give Oxygen	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Consider assisted ventilation <b>if required</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ensure appropriate positioning of the patient	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Identify and remove the</b> underlying source <b>of infection</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give analgesia	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give tetanus toxoid <b>(if exposed to tetanus)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give antipyretics	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Consider a blood transfusion <b>(if needed)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give low-dose steroids	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ensure appropriate location for care <b>(e.g. referral to hospital or HDU)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

6. Do you think any items are currently missing from the previous set of questions? If so, please comment below:

[illegible]

7. In your opinion, how **important** are the following in monitoring patients already identified as having severe maternal sepsis (within the first 3 hours), in low and low-middle income countries?

Please rate the following:

	1 = very un- important	2	3	4	5 = very important
Respiratory Rate & Heart Rate (using watch)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Temperature (using thermometer)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Blood Pressure(Systolic/Diastolic using sphygmomanometer)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Mean Arterial Pressure(using sphygmomanometer and calculator)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Conscious Level	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Urine Output (by catheter)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Capillary Refill	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Oxygen Saturation (by pulse oximetry)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Blood Glucose	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
Blood Culture ( <b>prior to commencing antibiotics</b> )	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
Culture of sample ( <b>e.g. lochia/urine/other swab</b> )	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
Microscopy/Gram staining ( <b>e.g. Pus or MSU</b> )	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
Haemoglobin	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
Lactate Level	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
C-Reactive Protein	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
White Cell Count	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
Platelets	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
Urea & Electrolytes	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
Clotting	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
PCV, haematocrit	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
Sickling	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
HIV rapid test	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	
Malaria testing	<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>		<input type="radio"/>	



Radiological Investigations (Chest XR, Abdominal XR or pelvic USS)

☐ ☐ ☐ ☐ ☐

Monitoring and treatment of baby if appropriate

☐ ☐ ☐ ☐ ☐ ☐ ☐

8. Do you think any items are currently **missing** from the previous set of questions? If so, please comment below:

9. How **feasible** do you think the use of the following will be in a **health centre** in a low and low-middle income country?

*(By a health centre we are considering a health facility which is aiming to provide basic emergency obstetric care. As such this is a facility where vaginal deliveries will usually take place, as well as routine antenatal and post-natal care but there is no recourse to caesarean section. There may be non-physician clinicians present as well as nurses and midwives; however it is unlikely there will be any doctors working at this sort of facility.)*

Please rate the following:

	1 = definitely un-feasible	2 = un-feasible	3 = feasible	4 = definitely feasible
Administer Intravenous Fluid	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Obtain venous access	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Administer antibiotics early	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Give Oxygen	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Consider assisted ventilation <b>if required</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ensure appropriate positioning <b>of the patient</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Identify and remove the</b> underlying source <b>of infection</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give analgesia	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give tetanus toxoid <b>(if exposed to tetanus)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give antipyretic	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Consider a blood transfusion <b>(if required)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give low-dose steroids	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Ensure</b> appropriate location for care <b>(e.g. referral to hospital or HDU)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Respiratory Rate & Heart Rate <b>(using watch)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Temperature <b>(using thermometer)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Blood Pressure <b>(Systolic/Diastolic using sphygmomanometer)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Mean Arterial Pressure <b>(using sphygmomanometer &amp; calculator)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Conscious Level	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Urine Output ( <b>by catheter</b> )	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Capillary Refill	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Oxygen Saturation ( <b>by pulse oximetry</b> )	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Blood Glucose	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Blood Culture ( <b>prior to commencing antibiotics</b> )	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Culture of sample ( <b>e.g. lochia/urine/other swab</b> )	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Microscopy/Gram staining ( <b>e.g. Pus or MSU</b> )	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Haemoglobin	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lactate Level	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
C-Reactive Protein	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
White Cell Count	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Platelets	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Urea & Electrolytes	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Clotting	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

PCV, haematocrit	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Sickling	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
HIV rapid test	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Malaria testing	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Radiological Investigations ( <b>Chest XR, Abdominal XR or pelvic USS</b> )	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Monitoring <b>and treatment of neonate if appropriate</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

10.

If you have any additional comments, please provide them below:

11. How **feasible** do you think the use of the following will be in a **district hospital** (or any facility where comprehensive essential obstetric care is available) in a low and low-middle income country?

Please rate the following:

	1= definitely un-feasible	2 = un-feasible	3 = feasible	4 = definitely feasible
Administer Intravenous Fluid	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Obtain venous access	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Administer antibiotics early	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give Oxygen	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Consider assisted ventilation (if required)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ensure appropriate positioning of the patient	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Identify and remove the underlying source of infection</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give analgesia	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give tetanus toxoid (if exposed to tetanus)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give antipyretic	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Consider a blood transfusion (if required)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give low-dose steroids	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ensure appropriate location for care (e.g. referral to hospital or HDU)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Respiratory Rate & Heart Rate <b>(using watch)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Temperature <b>(using thermometer)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Blood Pressure <b>(Systolic/Diastolic using sphygmomanometer)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Mean Arterial Pressure <b>(using sphygmomanometer)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Conscious Level	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Urine Output <b>(by catheter)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Capillary Refill	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Oxygen Saturation <b>(by pulse oximetry)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Blood Glucose	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Blood Culture <b>(prior to commencing antibiotics)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Culture of sample <b>(e.g. lochia/urine/other swab)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Microscopy/Gram staining <b>(e.g. Pus or MSU)</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Haemoglobin	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lactate Level	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
C-Reactive Protein	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>



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Thank you so much for completing this survey.

This survey will form the first stage of the Delphi process that will help us design the bundle. We would like to contact you again with a refined set of questions to reach consensus on the right components of the bundle.

If you are happy to be contacted again please enter your email address below, we will only contact you up to two more times as part of this process.



## APPENDIX 4: COPY OF ROUND THREE QUESTIONNAIRE

Following completion of the first and second rounds of the Delphi, we have arranged the top ranking elements in the below tables, applying a rank according to the mean score given for the importance for each element, as identified by both panels.

The steering committee have reviewed the responses for both practitioner and expert panels and found there was consensus on the five most important **treatment** elements.

**Figure 1:** The five most important **treatment** elements (and mean score) using results from both panels

Practitioner Panel	Rank	Expert Panel
<b>Antibiotics</b> Mean = 4.90, SD 0.58	<b>1</b>	<b>Antibiotics</b> Mean = 5.00, SD 0.00
<b>IV Access*</b> Mean = 4.83, SD 0.69	<b>2</b>	<b>IV Access*</b> Mean = 5.00, SD 0.00
<b>IV Fluids</b> Mean = 4.71, SD 0.76	<b>3</b>	<b>IV Fluids</b> Mean = 4.64, SD 0.48
<b>Source Control</b> Mean = 4.56, SD 0.82	<b>4</b>	<b>Location</b> Mean = 4.36, SD 0.34
<b>Location</b> Mean = 4.39, SD 0.97	<b>5</b>	<b>Source Control</b> Mean = 4.09, SD 1.16

\*IV access will be removed from the final ranking as it is intrinsic to two other top ranked elements (administration of IV fluids and IV antibiotics).

The steering committee also found there was consensus on the following seven most important **monitoring** elements.

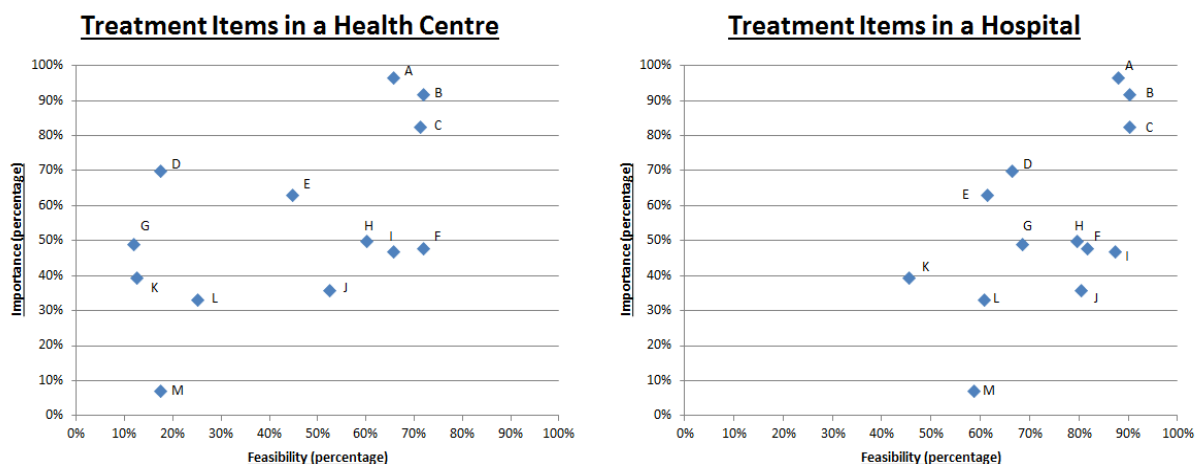
**Figure 2:** The seven most important **monitoring** elements (and mean score) using results from both panels

Practitioner Panel	Rank	Expert Panel
<b>Blood Pressure</b> Mean = 4.85, SD 0.58	<b>1</b>	<b>Respiratory Rate &amp; Heart Rate</b> Mean = 4.82, SD 0.39
<b>Respiratory Rate &amp; Heart Rate</b> Mean = 4.80, SD 0.70	<b>2</b>	<b>Conscious Level</b> Mean = 4.82, SD 0.39
<b>Urine Output</b> Mean = 4.73, SD 0.69	<b>3</b>	<b>Urine Output</b> Mean = 4.64, SD 0.48
<b>Conscious Level</b> Mean = 4.71, SD 0.71	<b>4</b>	<b>Monitoring of Baby</b> Mean = 4.64, SD 0.48
<b>Temperature</b> Mean = 4.65, SD 0.75	<b>5</b>	<b>Blood Pressure</b> Mean = 4.55, SD 0.66
<b>Monitoring of Baby</b> Mean = 4.46, SD 0.94	<b>6</b>	<b>Temperature</b> Mean = 4.27, SD 0.96
<b>Oxygen Saturation**</b> Mean = 4.38, SD 1.00	<b>7</b>	<b>Oxygen Saturation**</b> Mean = 4.27, SD 0.96

\*\* Oxygen Saturation was ranked highly in terms of importance but many practitioners reported it was not currently feasible in their setting. Following discussions at the WHO meeting in February, it was suggested that due to its importance this should be included, and recommended for use in those facilities where it was available.

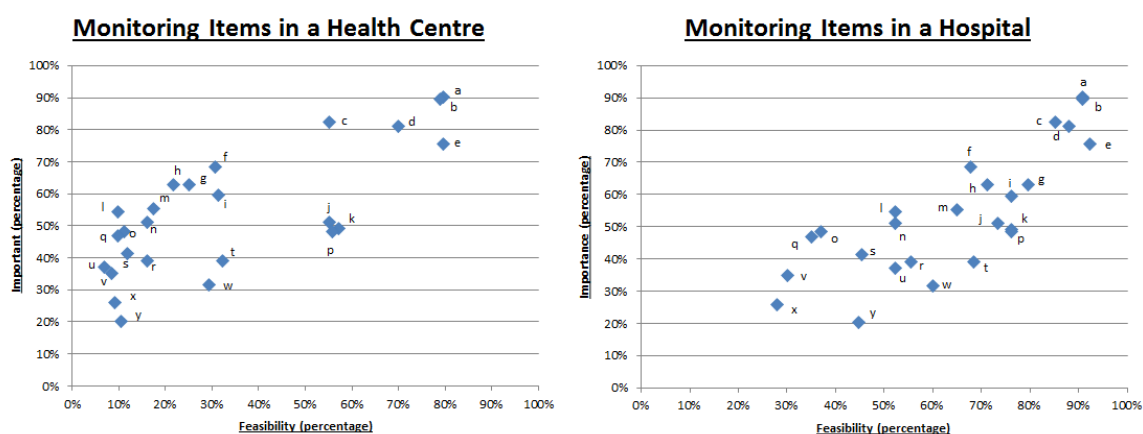
In addition to the tables above, please find below some figures showing further results from the first two rounds.

Figure 1 & 2 are scatter plots showing the importance against feasibility scores to show the trend for the elements in both hospital and health centre settings from round 1.



**Figure 1:** Scatter Plot showing the percentage of respondents who score an item as “definitely feasible” plotted against the percentage scoring the item as “very important” for treatment elements in both a health centre and hospital setting

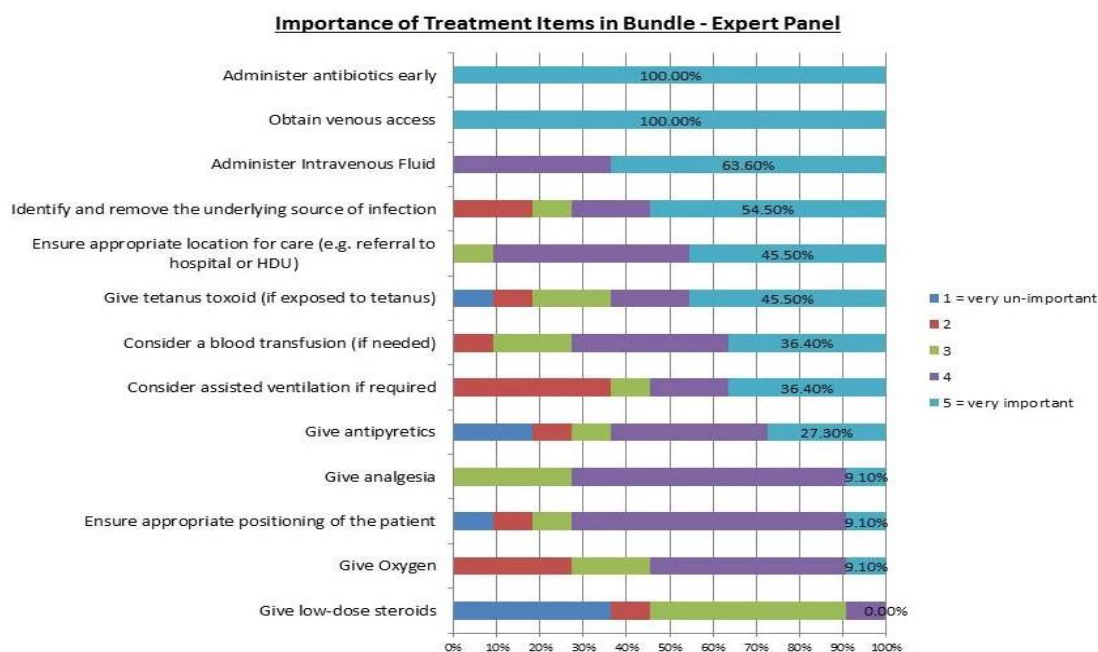
<b>A</b>	Administer antibiotics early	<b>H</b>	Give tetanus toxoid (if exposed to tetanus)
<b>B</b>	Obtain venous access	<b>I</b>	Ensure appropriate positioning of the patient
<b>C</b>	Administer Intravenous Fluid	<b>J</b>	Give analgesia
<b>D</b>	Identify and remove the underlying source of infection	<b>K</b>	Consider assisted ventilation if required
<b>E</b>	Ensure appropriate location for care (e.g. referral to hospital or HDU)	<b>L</b>	Give Oxygen
<b>F</b>	Give antipyretics	<b>M</b>	Give low-dose steroids
<b>G</b>	Consider a blood transfusion (if needed)		



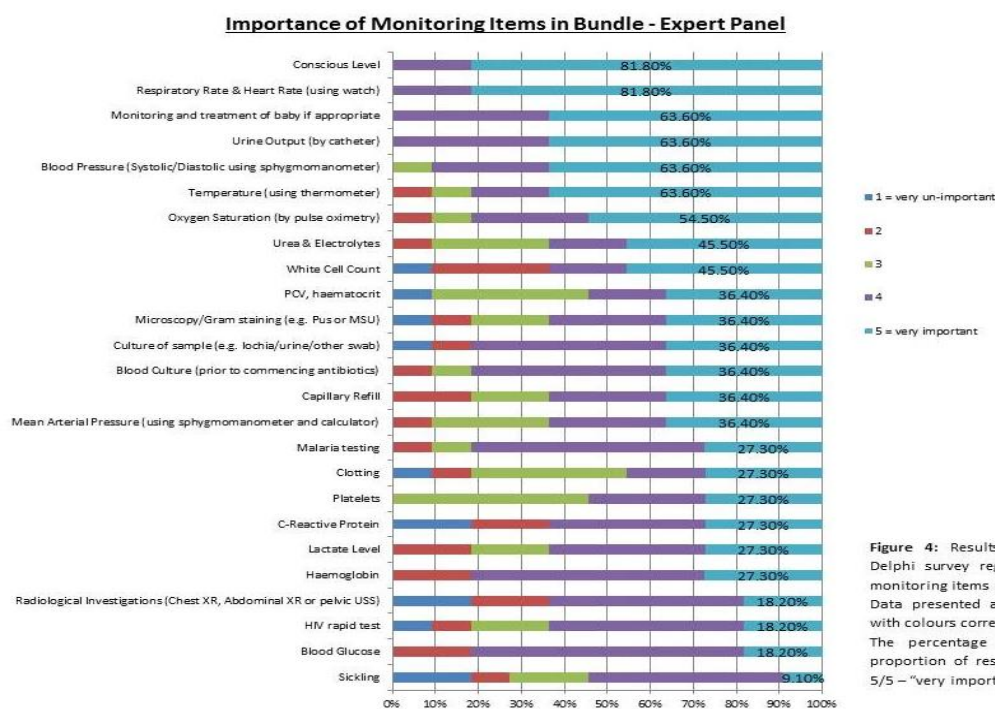
**Figure 2:** Scatter Plot showing the percentage of respondents who score an item as “definitely feasible” plotted against the percentage scoring the item as “very important” for monitoring elements in both a health centre and hospital setting

<b>a</b>	Blood Pressure (using sphygmomanometer)	<b>j</b>	HIV rapid test	<b>s</b>	Microscopy/Gram staining (e.g. Pus or MSU)
<b>b</b>	Respiratory Rate & Heart Rate (using watch)	<b>k</b>	Malaria testing	<b>t</b>	Blood Glucose
<b>c</b>	Urine Output (by catheter)	<b>l</b>	Urea & Electrolytes	<b>u</b>	Radiological Investigations (e.g. XR or USS)
<b>d</b>	Conscious Level	<b>m</b>	Platelets	<b>v</b>	Lactate Level
<b>e</b>	Temperature (using thermometer)	<b>n</b>	Clotting	<b>w</b>	Mean Arterial Pressure
<b>f</b>	Monitoring and treatment of baby if appropriate	<b>o</b>	Culture of sample (e.g. lochia/urine)	<b>x</b>	C-Reactive Protein
<b>g</b>	Oxygen Saturation (by pulse oximetry)	<b>p</b>	Capillary Refill	<b>y</b>	Sickling
<b>h</b>	White Cell Count	<b>q</b>	Blood Culture (prior to antibiotics)		
<b>i</b>	Haemoglobin	<b>r</b>	PCV, haematocrit		

Figures 3 & 4 are stacked bar charts showing the distribution of scores given in terms of importance of each item by our expert panel in round 2.



**Figure 3:** Results from the second round Delphi survey regarding the importance of treatment items using a Likert score out of 5. Data presented as 100% stacked bar chart with colours corresponding to the score given. The percentage highlighted indicates the proportion of respondents giving a score of 5/5 – “very important”



**Figure 4:** Results from the second round Delphi survey regarding the importance of monitoring items using a Likert score out of 5. Data presented as 100% stacked bar chart with colours corresponding to the score given. The percentage highlighted indicates the proportion of respondents giving a score of 5/5 – “very important”

Considering the above information, the key elements that were consistently found to be both feasible and important are as follows:

## IV Antibiotics

## IV Fluids

**Source** (identify source and source control)

**Location** (right facility and level of care)

**Monitoring of mother:** blood pressure/ respiratory rate/ heart rate/ conscious level/ temperature/ urine output/ oxygen saturations (if available) of **fetus/neonate**

1. Do you agree that the above key elements should be included in the final bundle? Please provide comments if you wish.

## Treatment Elements

23

## Monitoring Elements



Comments:

The screenshot shows a presentation window with a title bar at the top. Below the title bar is a large, empty rectangular area, likely for a slide or image. At the bottom of the window, there is a navigation bar containing several small icons: a left arrow, a square, a right arrow, and a vertical rectangle.

2. Are there any treatment or monitoring components you would like to **add** to the final bundle?

[illegible]

3. Are there any treatment or monitoring components you would like to **remove** from the final bundle?

[illegible]

Thank you so much for completing this survey. These results will form the important final part of the Delphi process. We will be sure to contact you again soon to update you regarding the final results.

## APPENDIX 5: EXECUTIVE SUMMARY OF MALAWI MEETING, MAY 2016



### Malawi In-Country Meeting Executive Summary Lilongwe, Malawi, 16-20<sup>th</sup> May 2016



#### Background:

Maternal sepsis is the third most common direct cause of maternal mortality accounting for 11% of maternal mortality worldwide (Say, 2014). A care bundle can be defined as “a small, straightforward set of evidence-based practices that, when performed collectively and reliably improve patient outcomes” (Institute for Healthcare Improvement, 2015). In high income countries, the introduction of care bundles has shown to double survival (Barochia, 2012 and Damiani, 2015). Unfortunately, there are no such bundles that are suitable for use in low-income countries.

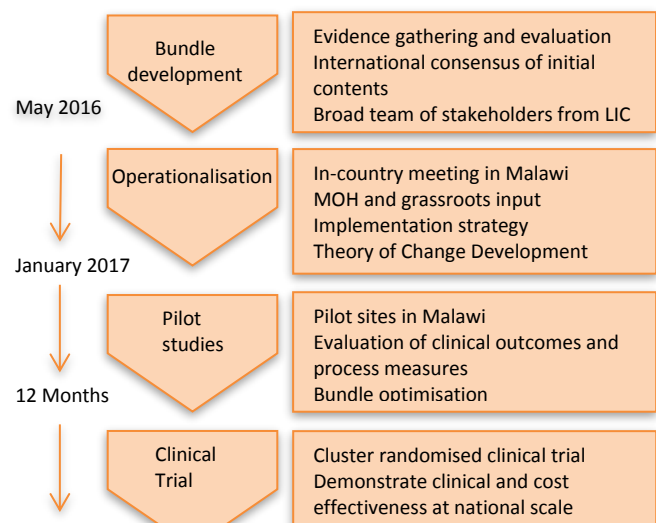


Figure 1: Flowchart diagram showing timeline for low-income maternal sepsis bundle project

As a team, we undertook a robust approach to develop a low-income maternal sepsis bundle that can be used in countries such as Malawi. This consisted of a modified Delphi approach, which engaged a broad range of LMIC practitioners and an additional international expert panel. The 3 rounds of the Delphi involved rating all potential bundle elements for both importance and feasibility in a LMIC hospital and health centre setting. This was then combined with feedback from in-person meetings of the WHO maternal sepsis working group. It was decided, in order to conclude the bundle development process, we would hold an in-country workshop meeting in Lilongwe in May 2016 to discuss the final components of our **FAST-M** bundle which consists of timely administration of **F**luids, **A**ntibiotics, **S**ource Control, **T**ransport and ongoing **M**onitoring (of mother and fetus/neonate). And how to operationalise and test this bundle.

#### Objectives of the meeting:

1. Discuss each of the final components of the bundle and its operationalisation at an in-country meeting in Malawi
2. Discuss and design a pilot study to assess the feasibility of the FAST-M bundle and its integration in the Malawian healthcare system
3. Ascertain potential sites for pilot study by carrying out site visits

### **In-Country Meeting: Bundle Summary**

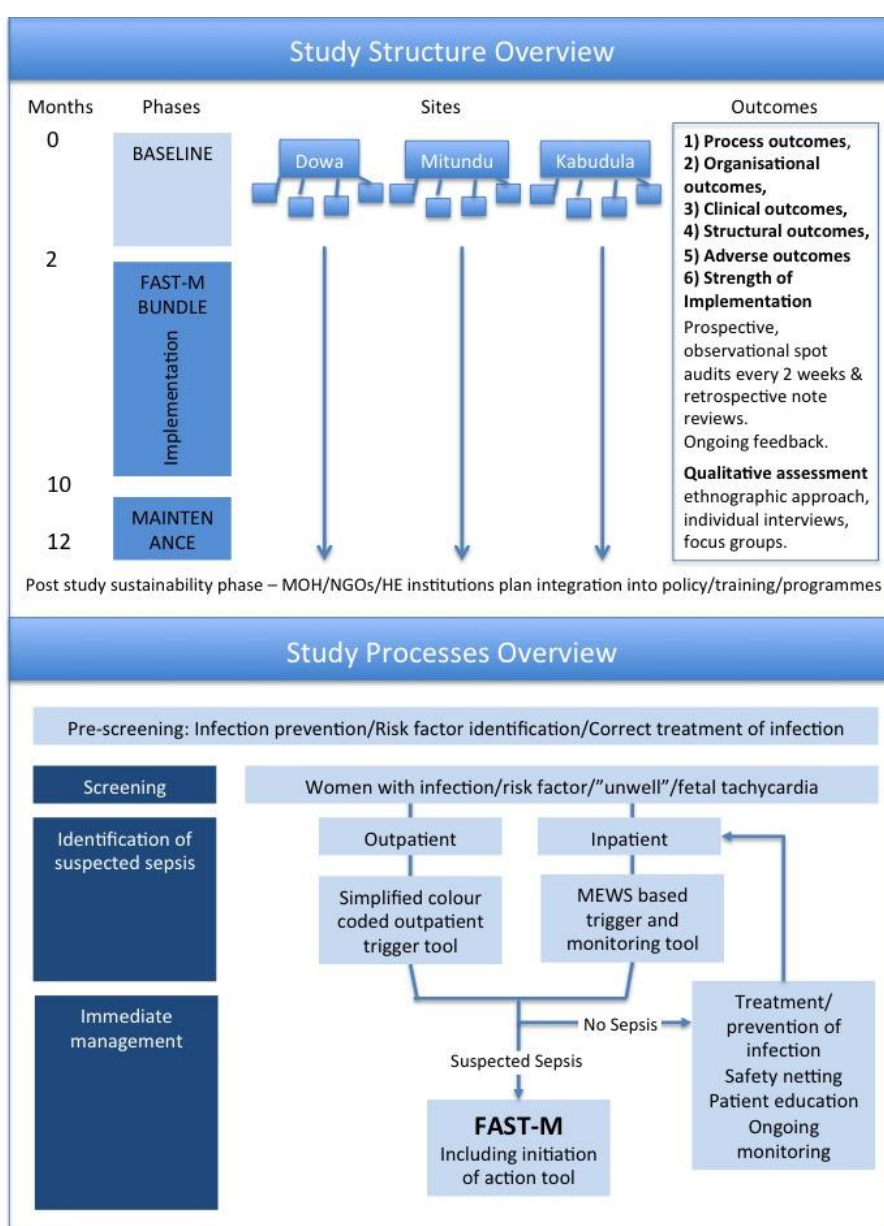
- The in-country workshop was held over three days (18-20<sup>th</sup> May) at Kamuzu Central College of Nursing (KCN) in Lilongwe, Malawi.
- Key representatives from a number of groups attended, including representatives from Malawi Ministry of Health (RHU), KCN, Malawi College of Medicine, Jhpiego Malawi Office, Malawi Association of Obstetric Clinical Officers (MAOCO), PACHI (Parent & Child Health Initiative), Save the Children, Global Sepsis Alliance/UK Sepsis Trust as well as a number of practitioners (nurses/midwives, clinical officers, obstetricians). A full list of delegates can be found in appendix 1.
- Individual meetings were held with representatives from UNICEF, DFID, Dr Charles Mwanswambo & the DHO for the Lilongwe region.
- As a group, agreement was reached on the final components of the FAST-M bundle.
- Each of the components were discussed in detail, identifying the challenges and solutions that will need to be considered. This information will go on to be used to create a theory a change, which will be a working model for use in the implementation of the bundle.
- During our discussion, we considered the ways in which we can make FAST-M easy to use and identified certain implementation tools that will be useful. This included visual aids in the form of cards and posters as well as regular team feedback. It was also highlighted that clinical audit and quality improvement would be helpful in allowing the healthcare professional to monitor their performance and encourage positive feedback.

### **In Country Meeting: Pilot Study Design Summary**

- Following discussion of the bundle elements, we considered the proposed pilot study, which is planned to take place for 12 months from January 2017. The idea of a feasibility study was well received and together, we developed important elements of the protocol as below:
- Feasibility Study Aim: To assess the feasibility of the FAST-M bundle and its implementation within the Malawian Healthcare System.
- Feasibility Study Objectives:
  - Demonstrate improvement in sepsis care (PRIMARY OBJECTIVE)
  - Gain insight about the delivery/implementation and use of bundle
  - Understand the existing gaps in services
  - User acceptability i.e. how do people like it
  - Identify barriers, strengths and solutions
  - Gather additional costs (e.g. stationary, petrol, instruments, additional staff)
  - Contribute to scaling up the study
  - Explore integration within Malawian Healthcare System

- Feasibility Study Outcomes:

- Strength of Implementation
- Survey or feedback to assess if people have understood
- Negative/adverse outcomes e.g. overuse of antibiotics
- Process outcomes including work on healthcare workers attitudes, knowledge, skills and narrative; monitoring adherence and compliance through a checklist.
- Clinical outcomes including: survival (mortality); neonatal outcome; hospital stay; complications and major morbidity
- Structural outcomes including: numbers of people attending training sessions, lack of supplies and human resources





**Site Visits:**

Site Visits were undertaken at the following health centres and hospitals: Daeyang Luke Hospital, Dzaleka Health Centre, Dowa Hospital and Mitundu Hospital. We held stakeholder meetings with clinical officers, nurse midwives and the DHO/DNO. We were able to establish the current practice for the management of obstetric patients with sepsis. In addition, we identified the barriers to providing care and explored some of the reasons behind these. We also introduced the new maternal sepsis bundle, and discussed its implementation.

**Action points from the meeting:**

A number of action points were identified upon culmination of the three day workshop, as below:

Action Point	Individual(s) Involved
Develop care pathway screening and action tool	UoB Team to draft and feedback from whole team
Develop onsite training/ skill drill materials	UoB Team to draft and feedback from whole team
Develop a FAST-M resource booklet	UoB Team to draft and feedback from whole team
Develop visual aids such as posters	UoB Team to draft and feedback from whole team
Develop work plan for source control and develop visual checkpoints for sources of infection (on a human figure)	UoB Team to draft and feedback from whole team
Develop broad guidance on fluid choice and rate of administration	UoB Team to conduct initial review, send to team for consultation, seek national Malawi and WHO team endorsement
Development of a template referral letter and standardised feedback system	UoB Team to draft and feedback from whole team
Develop mobile-based technology to support FAST-M including a website/app	UoB team to explore establishing partnerships and funding
Explore solutions to equipment supply issues and maintenance options	District Health Team and hospital administration (discussion with maintenance departments)
Task shifting to patient attendants to carry out monitoring roles if locally appropriate	Ministry of health, District health team and ward leadership teams
Identification of national and local maternal sepsis champions	Ministry of health, District health team and ward leadership teams
Encourage patient led behaviours	Ward leadership team
Explore how to improve/maintain communication between facilities and hospitals	Ministry, District health team and ward leadership teams
Maintain involvement of broader stakeholders (e.g. ministry and safe	District health team/Ministry of Health/DFID/College of Medicine &

motherhood, SRH	Nursing/JPIEGO/Save the children/UNICEF/MERK for Mothers
Explore learning about sepsis in pre-clinical training curriculum, other training schemes and explore FAST-M integration	College of Medicine/KCN/JPIEGO other NGOs
Develop dissemination plans for project end	UoB, with feedback from whole team
Develop marketing/ branding material	UoB Team + consultancy

### **Appendix 1:**

#### **Delegate List for Sepsis Bundle In-Country Meeting, Malawi**

- Arri Coomarasamy, University of Birmingham
- David Lissauer, University of Birmingham
- Abi Merriel, University of Birmingham
- Fatima Taki, University of Birmingham
- Amie Wilson, University of Birmingham
- Thomson Chirwa, Malawi Association of Obstetric Clinical Officers (MAOCO)
- Victoria Lweshu, Save the Children
- Chisale Mhango, Obstetrician from the College of Medicine
- Edward Scott Mhango, Malawi Association of Obstetric Clinical Officers (MAOCO)
- Laura Munthali, Nurse Midwife
- Bejoy Nambiar, Parent and Child Health Initiative (PACHI)
- Theresa Ngalawesa, Nurse Midwife
- Violet Manjanja, Nurse Midwife and Lecturer, Kamuzu College of Nursing
- Tambudzai Rashidi, JHPIEGO
- Limbika Taizi, JHPIEGO
- Pilirani Msambati, Reproductive Health Unit, Malawi Ministry of Health
- Charles Makwenda, Parent and Child Health Initiative (PACHI)
- Ron Daniels, Global Sepsis Alliance/UK Sepsis Trust

#### **Site Visit List of Delegates, Dowa Hospital, Malawi**

- Arri Coomarasamy, University of Birmingham
- David Lissauer, University of Birmingham
- Abi Merriel, University of Birmingham
- Fatima Taki, University of Birmingham
- Amie Wilson, University of Birmingham
- William Banda (NM technician PN ward)
- Gift Sinoya (CO/nutritionist)
- Elizabeth K (NM PN ward)
- David Nkoma (auxiliary nurse PN ward)

- Zolane Thom (NM)
- Lozalia Modiza (NM)
- Veronica Banda (NM)
- Pearson Tembo (NM)
- Themy Temwa
- Ulemu Chyada
- Dorothy Imau
- Chikonde Ntaya (deputy DNO)
- Blessings Kumundu (nurse supervisor/in-charge)

Site Visit List of Delegates, Mitundu Hospital, Malawi

- Arri Coomarasamy, University of Birmingham
- Abi Merriel, University of Birmingham
- Amie Wilson, University of Birmingham
- Fatima Taki, University of Birmingham
- David Lissauer, University of Birmingham
- Ron Daniels, Global Sepsis Alliance
- Emmanuel (CO and in-charge)
- A number of other nurse/midwives/technicians and a ward clerk from the maternity unit